Photochemical Control of Pyramidal Inversion

and

Photoactivation of Antimicrobial Agents

Submitted by

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CONTENTS

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ABSTRACT

Control of molecular motion is an important step towards the envisaged development of molecular scale devices and machines. A large amount of research has been documented regarding the control of molecular rotation and shuttling processes, but relatively few examples of control over nitrogen pyramidal inversion exist and so far no examples that require solely physical inputs such as light and heat have been reported. The first part of this thesis describes attempts to control nitrogen pyramidal inversion in aziridines and azetidines, using only light and heat to switch between two states with differing rates of inversion. Three avenues of research utilising anthracene photochemistry are discussed. The strategies employed include modifying ring strain by fused macrocycle formation; introduction of ring strain *via* small ring formation; and disruption of transition state stabilising hydrogen bonds through macrocycle formation. Finally, and more successfully, azobenzene photochemistry was used to modify a π-system adjacent to an aziridine nitrogen centre resulting in different inversion rates in the *cis* and *trans* azobenzene isomers. The experimentally derived inversion rates were supported by *ab initio* calculations.

The second part of this thesis outlines attempts to develop photoactivated *β*-lactam antimicrobial agents. Two families of compounds were synthesised, based on amine linked *bis*-anthracene, and 2-pyridone isomerisations. Their antimicrobial activity was evaluated against *B. Subtilis* and *E. Coli* using the Kirby-Bauer disk diffusion method. One *β*-lactam produced by anthracene photodimerisation displayed modest activity against *B. Subtilis.* However, control experiments suggested the acyclic precursor possessed higher levels of antimicrobial activity.

DECLARATION

Except where clearly indicated, the work reported in this thesis is an account of my own independent research at the University of Warwick carried out between October 2008 and August 2012.

The research reported in this thesis has not been submitted, either wholly or in part, for a degree at another institution.

ABBREVIATIONS

Ac	Acetyl
Anal.	Analysis
Ar	Aromatic ring
atm	Atmosphere
Bn	Benzyl
br	Broad
ca.	*Circa*
Calcd.	Calculated
CAN	Ceric ammonium nitrate
cat.	Catalytic
CCD	Charge-Coupled Device
δ	Chemical shift
d	Doublet
dd	Doublet of doublets
E	Electrophile
EI	Electron Impact
ee	Enantiomeric excess
ESI	Electrospray Ionisation
equiv.	Molar equivalents
EWG	Electron-withdrawing group
EXSY	Exchange spectroscopy
GS	Ground state
h	Hour(s)

HCl	Hydrochloric acid
HMBC	Heteronuclear Multiple Bond Connectivity
HMQC	Heteronuclear Multiple Quantum Coherence
HRMS	High Resolution Mass Spectroscopy
IPA	*iso*-Propyl Alcohol
IR	Infrared
L	Ligand
LA	Lewis acid
LMCT	Ligand to Metal Charge Transfer
Lit.	Literature
µ	micro
m.p.	Melting point
m	Multiplet
m-CPBA	*meta*-chloroperoxybenzoic acid
Ms	Methane sulfonyl
MS	Mass Spectrometry
Napth	Naphthyl
min.	Minute(s)
NMO	*N*-Methylmorpholine-*N*-oxide
Nu	Nucleophile
NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser Effect
p-	*para*-
PMB	*para*-methoxybenzyl
ppm	Parts per million

Py	Pyridine
q	Quartet
R_f	Retention factor
r.b.f	Round bottom flask
rt	Room temperature
rtp	Room temperature and pressure
s	Singlet
S_N2	Bimolecular nucleophilic substitution
t	Triplet
$t_{1/2}$	Half-life
Temp.	Temperature
Tf	Trifluoromthanesulfonyl
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TM	Target molecule
TMS	Trimethylsilyl
TS	Transition state
Ts	*para*-toluenesulfonyl
w/v	Weight per unit volume
xphos	2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl

Chapter 1:

Photocontrol of Molecular Motion

1.1 Introduction

1.1.1 Importance of Molecular Devices and Machines

The greatest improvements in the productivity and standard of living for the human race have derived directly from the invention and subsequent development of novel devices and machines. For most of history this has focused around mechanical machines, however in more recent times the greatest advancements have come from the development of electronic devices and computer controlled machines. A device is defined as something which is created for a specific purpose, whilst a machine is any combination of mechanisms designed to utilize, modify, apply or transmit energy.[1] This concept can also be applied on a molecular level as it is possible to arrange a number of molecular components in such a way that it gives the overall assembly a specific purpose such as reactivity, or can do useful work such as directional rotation or ratchet like movements.[1]

The development of any molecular devices or machines faces adversity in the form of powerful random thermal Brownian motion and dominant viscous forces. The challenges to creating useful molecular devices often seem insurmountable, however evidence that it can be achieved is all around us in every biological system imaginable.[2] Central to the development of these new devices is the control of many different modes of molecular motion which can be modified by external inputs and applied in a way to fulfil a useful function.

1.1.2 Application of Molecular Devices and Machines

If developments in electronic devices are to continue, the power of computer processors and memory density must correspondingly increase.[3] Currently, all of these devices are silicon based and comprise of millions of individual transistors that are created on single crystals of silicon using nano lithography techniques. These production methods continue to evolve and the size of the transistors that can be produced has fallen as low as 22 nm, allowing 1.4 billion transistors to be fitted on an area of only 160 mm^2.[2,4] However, current methodology can only go so far before the classical mechanics of bulk materials become overshadowed by quantum mechanical properties of small dimensions and the systems fail to function.[5]

Small molecules are measured in the order of Ångströms, which are many orders of magnitude smaller than current transistors. If molecules could be created which allowed for a reversible transformation between two stable states that could be easily differentiated, then a molecular transistor or switch could be created.[6]

Hope also lies in the ability to synthesise molecules capable of doing mechanical work in the same way as macroscopic machines.[7] The control of molecular motion, such that there is control of direction, amplitude and rate of movement rather than random Brownian motion, is crucial in this application.[8] Particular attention has been paid to molecules which can contract and expand in the hope that synthetic muscles can be synthesised. Directional control of rotation, to form motor like molecules, and meshed rotors, which provide gearbox like functionality, are important steps towards molecular machines. However, fundamentally, all of these systems require some

form of switching mechanism that allows control between the different states of motion.[7]

1.1.3 Literature Examples

1.1.3.1 Small Molecules

There are numerous examples of configurational changes in small molecules, some of which are shown in Figure 1.1. These can take the form of a wide variety of transformations, from ring formations to isomerisations but, importantly, they must be stable in two or more different configurations and the interconversion must be reversible. A great benefit of these simple small systems, is that it is commonly possible to achieve this without the use of chemical reagents, as many systems can be controlled using physical inputs such as light and heat. Amongst the most common examples, is double bond *cis-trans* isomerisation. Whilst the amplitude of the motion is often not significant enough for use as a molecular machine on their own, they offer excellent photoactive handles for use as molecular switches, or as a control receptor in larger molecular machines.[9] These are some of the most studied systems, with stilbenes having been investigated for over 55 years,[10] and commonly display distinct physical changes between states such as colour changes.

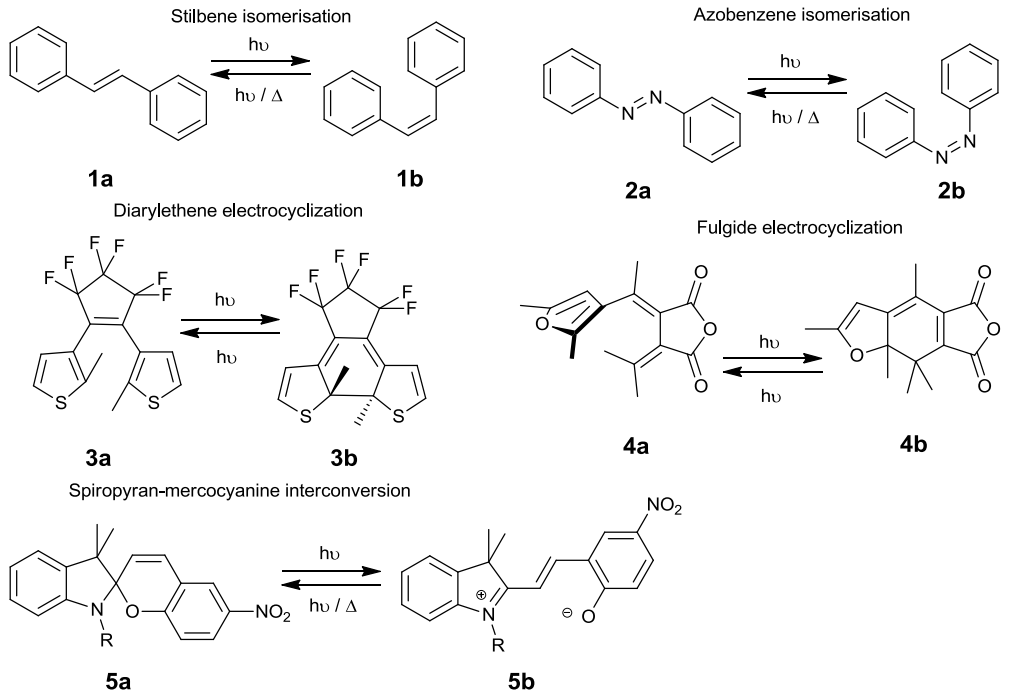


Figure 1.1. Common photochromes used extensively as molecular switches and other devices, figure reproduced from Angewandte Chemie Int. Ed.[7]

These compounds have been used in many applications which rely on changes to the 3-dimensional structure and, when used to control the shape of larger molecules, the rather insignificant motion of the subunit is amplified over the much larger molecule. Often these molecules are used as part of larger switching systems based on binding or interlocked systems. The small molecule fragment is used as the photochrome switch which changes the tertiary shape of a larger molecule, turning a binding or shuttling process on or off.[11] Gust *et al*[12] has taken the simple molecular switching properties of these small molecules and, by covalently linking them to other chromophores in a fashion which allows either electron or energy transfer, has turned them into much more complicated molecular logic operators with many more potential states.

Azobenzenes in particular have been put to great use in a wide variety of applications. Koshima *et al*[13] have shown that whilst the amplitude of the isomerisation motion may be small, it has a significant effect on crystal packing. They irradiated the (001) face of large, thin platelet crystals of *trans*-4-(dimethylamino)azobenzene which had one end fixed to a glass substrate. Observations using a CCD microscope showed the crystals bending away from the light source and then returning to their original position a few seconds after irradiation ceased. Importantly, this could be repeated hundreds of times with no detrimental effect on the crystal (Figure 1.2).

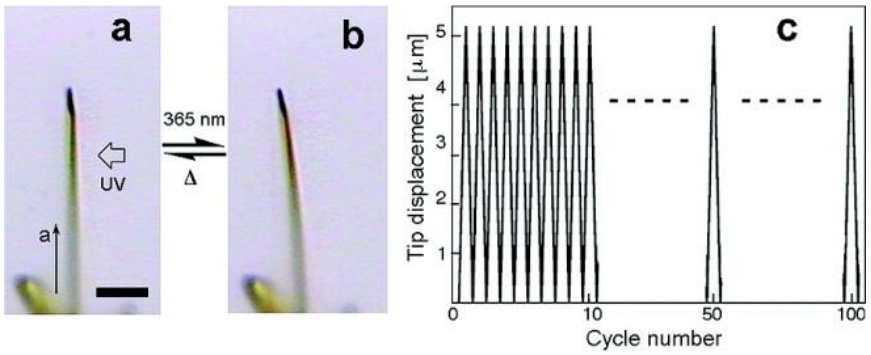
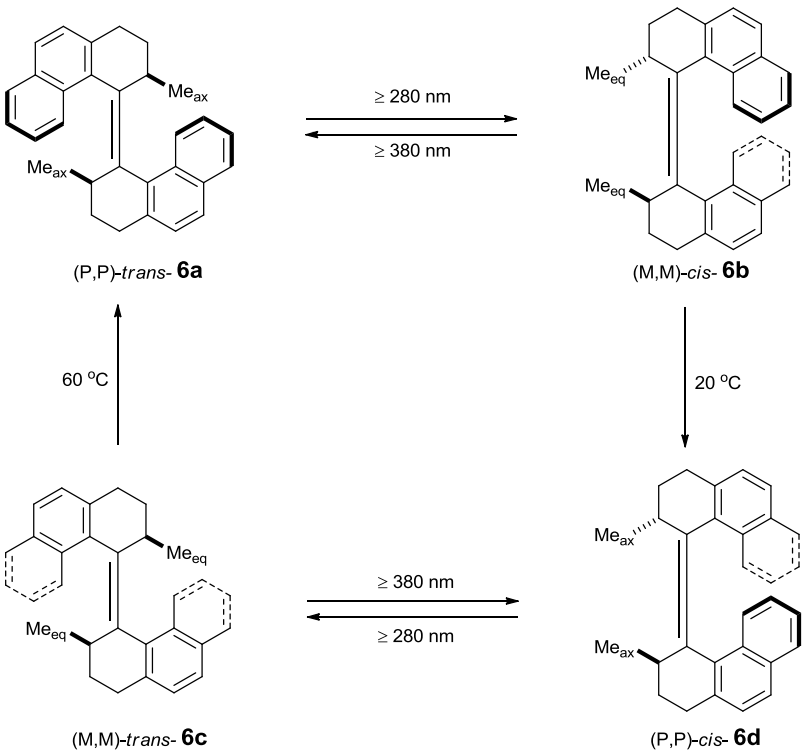


Figure 1.2. Bending a crystal using the isomerisation of azobenzenes, the process can be cycled many times as demonstrated by Koshima *et al*, figure reproduced from the Journal of the American Chemical Society.[13]

These small molecule fragments have also been used to create biological switches, where the activity of important biological molecules can be turned on or off.[14] As biological systems are widely regarded as being the most advanced form of molecular machines and devices, the ability to gain control over these highly evolved molecular systems is a significant step forward. Many examples incorporate azobenzenes or spiropyrans into existing biological molecules, and the new molecules are initially tested to ensure the modification has not disrupted the bioactivity. The switching of the photochrome is then expected to significantly alter

the tertiary structure of the molecule so that it is no longer able to partake in the necessary binding interactions to fulfil its biological role.[11,15]

Control of bond rotation has been an area of great interest due to the obvious similarities with mechanical motors. There are many examples of bond rotations, in fact almost all single bonds are freely rotating. The great difficulty comes from controlling this so that there is specific directional control above the random thermal motion. This motion is common in biological systems[16] but surprisingly hard to reproduce synthetically. The first example of this by Feringa *et al*[17,18] requires four isomerisations using ultraviolet light and heat in order to complete 360^{o} of rotation (Scheme 1.1). The axial chirality and two chiral centres were found to be instrumental in the directional control of the rotation. Isomerisation of the alkene allows for rotation through 180^{o}, and a thermally controlled helical inversion allows continued rotation, preventing rotation in the wrong direction.



Scheme 1.1. Feringa's uni-directional switch requires four steps to complete one 360^{o} rotation, scheme reproduced from Nature.[18]

There are some examples of small molecule switches being applied to surfaces in order to reversibly alter the surface properties on demand. A notable example is the alteration of the wetting properties of glass surfaces using spyropyrans. The contact angle of water droplets was measured on glass surfaces before and after irradiation with UV light. After irradiation with UV light, the contact angle was found to decrease by 14^{o} as the surface wetted easier, whilst irradiation with visible light returned the glass to its original properties.[19] Self-assembled monolayers of rigid azobenzenes on gold surfaces have been used in a number of devices. Ferri *et al*[20] have used conducting azobenzenes between two electrodes as a photocontrolled current switch, since the distance between the terminus of the molecule and the electrode can be changed by the *cis* to *trans* isomerisation (Figure 1.3).

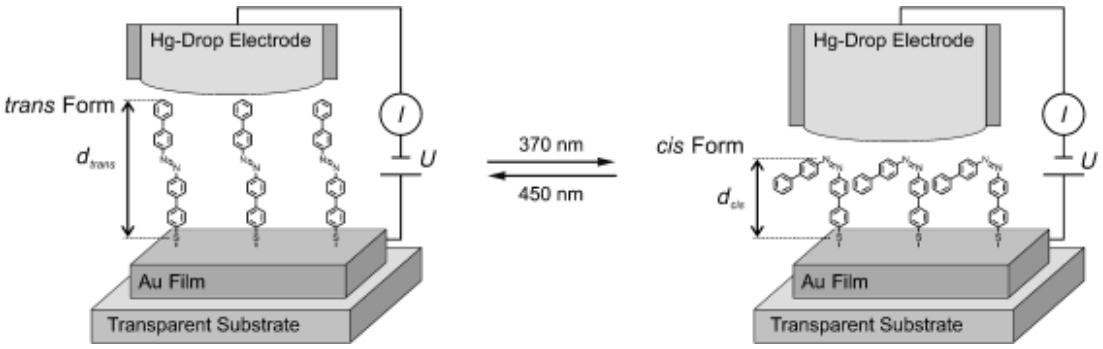


Figure 1.3. Ferri demonstrates the use of azobenzene isomerisation as an electronic transistor, figure reproduced from Angewandte Chemie Int. Ed.[20]

1.1.3.2 Interlocked Systems

The control and application of motion to interlocked supramolecular systems has seen massive progression in recent years.[21] Developments in synthetic techniques, the stability, and the flexibility of these systems has made them very popular targets for a variety of applications.[22] Rotaxanes are molecules where a threaded cyclic "ring" molecule is trapped on a linear "axle" by bulky terminal stopper groups, but is not connected to the axel by covalent bonds. Catenanes are compounds comprised of two mechanically interlocked ring systems. Both of these have been put to great use as examples of controlled molecular motion and as molecules capable of doing useful work. Shuttling processes in both of these systems are the crucial motif, and dominate their use in these systems.[23]

Shuttling is brought about by engineering two or more segments of the linear axle molecule, where there is a stabilising interaction with complementary functional groups on the captive ring molecule. In many cases the interaction of the sites with the ring is similar, but there is a small barrier between the lower energy positions which leads to degenerate rotaxanes where both states are equally populated. If it is possible to alter the strength or favourability of the ring's interaction with one or

other of the binding sites using any external stimuli, be that chemical or physical, then the molecule becomes a molecular switch (Figure 1.4). However, due to the larger size of these molecules and their very mechanical nature, the application of these molecules has developed far beyond simple switching systems. The applications of this control of molecular motion are very broad and seemingly only limited by the imagination of their inventors.

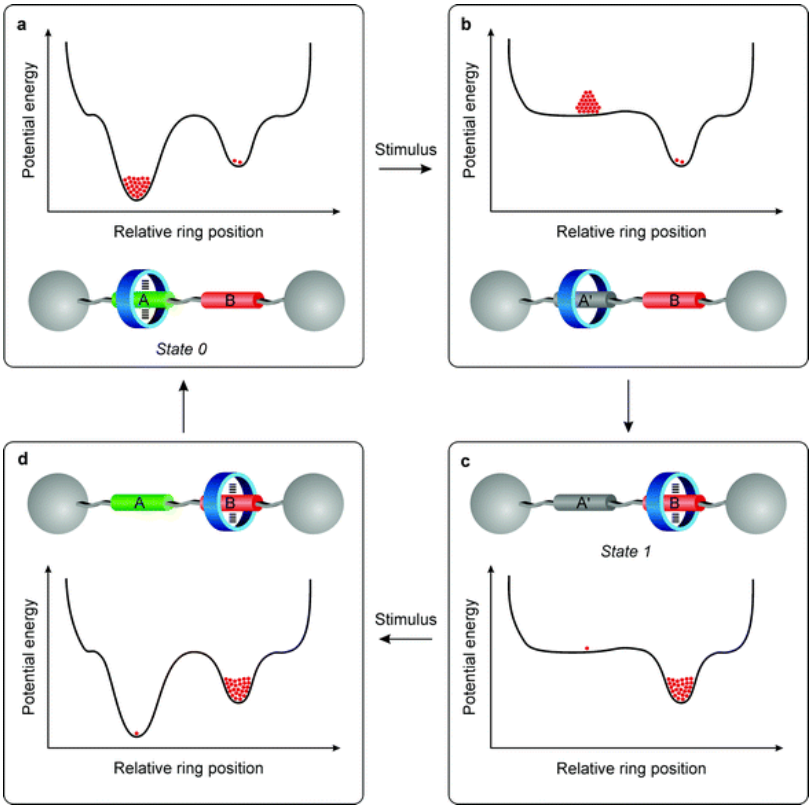


Figure 1.4. If the interaction between the macrocycle and axle site can be modified or blocked, it becomes possible to modify the potential energy surface forcing the bulk of the molecules to switch site positions. Figure reproduced from the Journal of Materials Chemistry.[24]

Examples of molecules that exhibit muscle and lift like motion have been demonstrated in solution, which requires the use of chemical inputs.[25-27] These are most commonly operated by changes in solution pH and have proven to be very effective. Similar systems exist that do not require chemical inputs but are instead controlled by physical inputs such as light[28] and electrochemistry.[29] However, due to

increased complexity in design, their function is commonly not as advanced as in chemical-based systems.

The most significant advancement with interlocked systems has come from the ability to arrange them on surfaces, which has been used in many applications to functionalise surfaces, achieve useful work and alter bulk properties. Berná *et al*[30] have shown great ingenuity by using a simple photo-promoted shuttling rotaxane to modify the hydrophilicity of the surface. A self-assembled monolayer of 11-mercaptoundecanoic acid on a Au(111) surface was coated with the rotaxane, which was held in place by a hydrogen bonding interaction with the carboxylic acid of the monolayer. One station is fluorine rich with a weak interaction with the ring. However, there is a stronger interaction with the fumaramide subunit, causing the fluorine rich zone to be exposed. Irradiation with UV light causes a 50% isomerisation of the fumaramide to maleamide, which has a very poor binding affinity for the ring. This causes 50% of the molecules to shuttle to the fluorine zone, causing an increase in hydrophilicity of the irradiated area. By irradiating the area along the leading edge of a liquid droplet, it was possible to encourage the droplet to move in that direction. Using this technique it was possible to move a 1.25 µL liquid droplet of diiodomethane along a surface and even up gradients of 12^{o}.

Mimicking the action of biological muscles with molecular machines has always been of great appeal as it relates so closely with the action of the human body. Whilst creating interlocked systems which are able to resemble some macroscopic movements has been successful, the action of a muscle requires directional orientation and complex attachment to a surface. This has been demonstrated by Liu

and co-workers in the form of a linear controlled muscle, based on a rotaxane (Figure 1.5).[31]

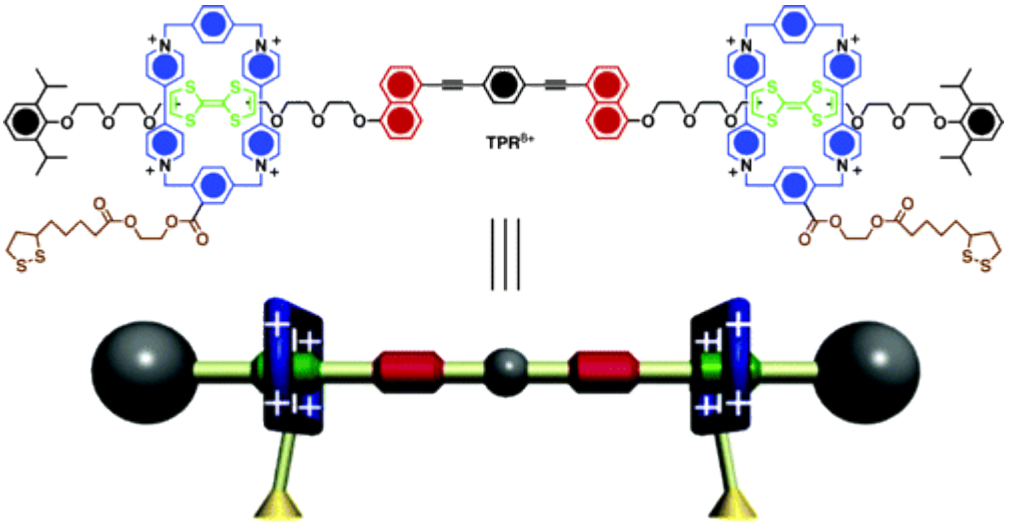


Figure 1.5. A symmetric rotaxane where the two rings are bonded to a gold surface by the thiol linkers. Redox chemistry can be used to shuttle the rings which causes a contraction to occur. Figure reproduced from the Journal of the American Chemical Society.[31]

Figure 1.5 illustrates how the muscle works. Redox chemistry controls which site is preferred, the rings are tethered to a gold surface in the extended position and when the rings move to the alternate position, this forces a contraction of the muscle. This has been successfully demonstrated on a very thin gold cantilever where one side was coated with a layer of this compound. Activation resulted in a measurable deflection of the cantilever.

1.1.4 Challenges

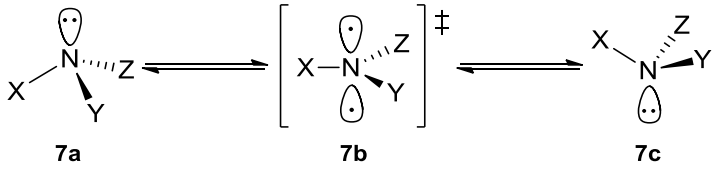
There are a number of challenges faced by molecular scale systems and one of these relates to the stability and reactivity of individual molecules. Commonly, the bulk is what is measured, with the results and compound stability coming from a statistical analysis of a very large number of molecules. Researchers have worked around this by using relatively small matrices of molecules and taking results from the average output of the matrix.[32]

A large amount of progress has occurred over the last 20 years. Many of these literature examples have demonstrated how chemists are now able to design and synthesise highly innovative molecular systems. The design of compounds which allow for the control of molecular motion has become more advanced, however the next step needs to be taken to integrate the molecules into more complex environments. Attachment of molecular devices to bulk materials to do useful work can be difficult. Control over their orientations so that they are ordered allows the molecular motions to be combined, causing a macroscopic effect.

Finally, many systems reported so far are dependent on the addition of chemical reagents, or "fuel", to switch between states. This causes a large amount of waste, but also limits the number of possible cycles before samples either become too diluted or degradation occurs. Ideally, the use of physical inputs is attractive, potentially allowing endless cycling and also allowing the systems to be taken out of solvent so that they become easier to implement into solid-state devices.

1.1.5 Pyramidal Inversion

Much of the recent published research has been directed at controlled rotation around atomic bonds and supramolecular interactions, such as rotating rings and shuttling processes. Very little effort has thus far been put towards control of the lever like motion of nitrogen pyramidal inversion. If a tricoordinate molecule exists in a non planar ground state, it becomes theoretically possible that it can exist in two distinct geometric configurations (Scheme 1.2). These configurations are then interchangeable by transposition of the substituents to the opposite side of the central atom, thereby forming a mirror image of the original molecule. This process is given the name pyramidal inversion, from the pyramidal shape of the molecules involved and the fact that the net result is inversion of the stereochemistry at that centre. Whilst there are many possible mechanisms by which this process may occur,[33] those of interest here do not involve the making and breaking of atomic bonds, nor excitation from the electronic ground state.



Scheme 1.2. Nitrogen Pyramidal Inversion.

There are two competitive modes by which pyramidal inversion can proceed. A classical vibrational pathway proceeds through a planar transition state, the rate of which is dependent on the relative populations of vibrational energy levels above and below the potential energy barrier to inversion. By non classical methods, inversion is believed to occur *via* quantum mechanical tunnelling from one side of the activation barrier to the other. In practice, for pyramidal inversion this pathway only

becomes significant when one of the substituents of the central nitrogen atom is hydrogen or deuterium, and at temperatures where vibrational energy levels within 6 kcal mol^{-1} are heavily populated.[33] In the context of the research described in this thesis, it is assumed that the classical vibrational pathway is dominant and that where inversion rates between systems are compared, the quantum mechanical rate contribution remains consistently small due to the substituents remaining constant and of significant mass.

The research in this thesis is focused on systems where nitrogen is the inversion centre. Nitrogen pyramidal inversion, also called "umbrella motion", has been the subject of much experimental and theoretical investigation since it was first observed in 1929.[34] The process derives from the rapid oscillation of the lone electron pair in trisubstituted amines through the X, Y, Z, plane resulting in the formation of the opposite enantiomer (Scheme 1.2). Due to the low barrier to pyramidal inversion, the process takes place rapidly at room temperature for ammonia and other simple amines. The nature of the X, Y and Z substituents can greatly affect the rate of this process through a number of different mechanisms.

1.1.6 Rate Controlling Factors in Pyramidal Inversion[33,35,36]

1.1.6.1 Isotope Effects

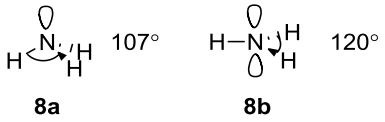
Substitution of the inversion centre with many different isotopes has been shown to have no significant effect on inversion rates. Similarly, isotope substitution on large groups such as CH_3 to CD_3 also made no measurable difference to inversion barriers. However, when an NH aziridine was compared with an ND aziridine, the activation energy was found to increase by 3 kcal mol^{-1}.[33] This difference is due to the significant proportion of inversion due to tunnelling in NH aziridines, because the probability for a particle to tunnel into the classically forbidden region declines exponentially with the mass of the particle. The doubling in mass between hydrogen and deuterium is the most significant change in mass between isotopes of the same element and is one of the few examples where the mass of the substituent is low enough to make quantum mechanical tunnelling significant.

1.1.6.2 Strain Effects

There are two significant strain effects to consider. When two of the substituents are connected to form a ring, there becomes a discrepancy between the actual and ideal bond angles. Little strain is observed in six membered rings, however, as the rings get larger or smaller, the strain increases as deviation from the ideal bond angle increases.

If the inverting atom forms part of a small ring, the resulting ring strain is greater in the transition state than in the ground state. This is due to a greater deviance from the desired bond angle (Figure 1.6). In aziridines the bond angle is constrained to 60^{o}

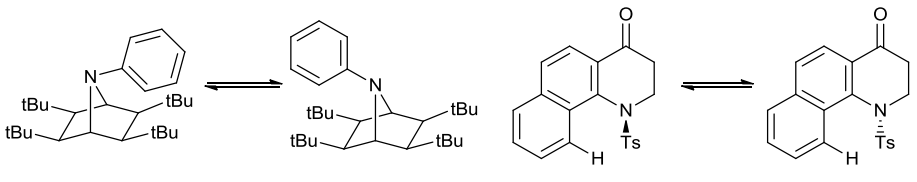
and, as the nitrogen hybridization changes from sp^3 (107^o) to sp^2 (120^o) in the ground state and transition state, the deviation from the ideal angle increases. This destabilizes the transition state relative to the ground state, making the activation energy larger and therefore the inversion rate slower.



8a **8b**

Figure 1.6. Bond angles.

Steric strain is also an important factor. Non-bonding repulsions can cause either acceleration, or slowing of inversion, depending on whether the interaction is strongest in the ground state or transition state. Most commonly, steric interactions in the ground state are observed when the Van der Waals volume of the inverting substituent becomes larger. These interactions are relieved somewhat in the sp^2 transition state due to the increased angular separation (Scheme 1.3). The non-bonding interactions in the ground state increase its energy relative to the transition state, thereby lowering the activation barrier. Occasionally, more distant sectors of a molecule may sit in the same plane as the inversion transition state, causing the same but opposite effect as a result of steric strain in the ground state (Scheme 1.3).



9a **9b** **10a** **10b**

Scheme 1.3. Left, steric crowding in the ground state. Right, steric destabilisation of the transition state.[33]

1.1.6.3 Conjugative Interactions

A molecular π-orbital on a substituent attached to the inverting centre allows for conjugation of the nitrogen's lone pair. In the ground state, the lone pair occupies an sp^3 orbital whereas in the transition state the lone pair sits in a pure p-orbital. The overlap of the π-orbital and the p-orbital is much better than with the hybridized orbital, allowing for greater conjugation and therefore increased stabilization of the transition state compared with the ground state (Figure 1.7). This effect is strongest when the substituent is –COR, –NO or $–NO_2$ because the orbital energy overlap is greatest.[33]

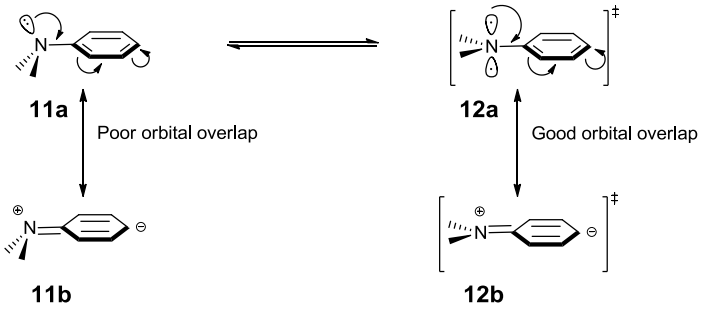
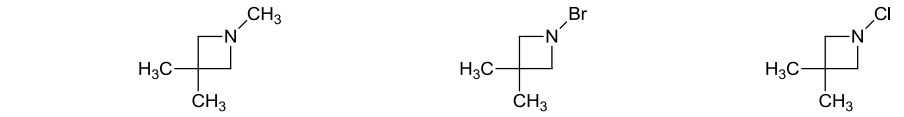


Figure 1.7. Stabilization of the transition state by increased resonance.

1.1.6.4 Inductive Effects

Replacement of a nitrogen substituent for a more electronegative one results in an increase in the free energy of activation. This is demonstrated in the series shown in Figure 1.8. An increase in s character of the hybridized non-bonding orbital in the ground state causes stabilization. As the transition state lone pair rests in a purely p orbital, no stabilization can be obtained.[33]



$\Delta G^{\ddagger}$ (kJ mol^{-1})	35.5 ($CFCl_3$)	48.1 (CH_2Cl_2)	49.8 (CH_2Cl_2)
T_c (^{o}C)	- 98	- 56	- 47
	13	**14**	**15**

Figure 1.8. The effect of induction on pyramidal inversion.[33]

1.1.6.5 Bonding and Complexation

Association of the ground state lone pair in coordination or bonding interactions retards inversion. Commonly, this causes inversion to halt when a strong bond is formed, such as protonation of the nitrogen atom. Because the stabilizing interaction must be broken before inversion can occur, the barrier rises by a similar amount to the strength of the bonding interaction (Figure 1.9). Similarly, any bonds formed in the ground state that will impart additional strain reaching the transition state or opposite invertomer, will raise the barrier to inversion.

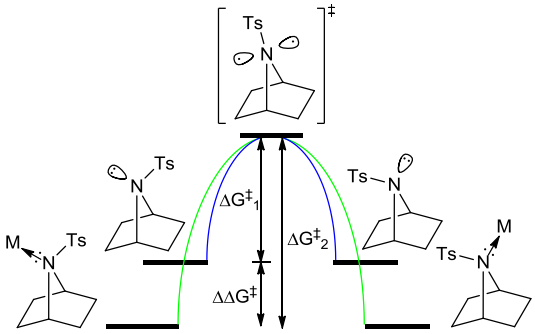


Figure 1.9. Ground state stabilization through lone pair interactions.

1.1.7 Inversion Rate Determination[33,37-39]

The ring strain inherent in small rings causes an increase in the activation energy of inversion, due to additional ring strain energy when progressing from the sp^3 ground state to sp^2 transition state. This is very important as it slows the rate of the inversion process to such an extent that it becomes similar to the NMR time scale, allowing the rate to be probed using variable temperature NMR techniques. Three different methods have been developed to extract rate data from VT-NMR spectra, and all of them have been shown[40-42] to provide reliable data as long as some requirements are met for each method. Where possible, a combination of these methods is used to further validate the results and assist with error analysis.

1.1.7.1 Coalescence Temperature Calculations

The quickest and simplest method requires knowing only the fully resolved signal separation and temperature at which the signals coalesce. Using Equations 1.1 and 1.2, the rate and activation barrier of the process can be calculated at the coalescence temperature. Under ideal conditions, this method has been shown to yield very accurate data, however, there are a number of requirements. There must be no contaminant or interfering signal between those being studied as this adds uncertainty with respect to the determination of the coalescence temperature. It must also be possible to reach a temperature where the separated signals are fully resolved in order to determine the maximum signal separation. The two species being studied must also have equal populations and the signals must be uncoupled. This method has been used on hydrogens which are coupled, but this can only be assumed to yield an approximation as one of the simplifications that yields this equation is that the

signals are not coupled. Unfortunately, one of the major drawbacks of this method is that it is only possible to calculate the rate and $\Delta G^{\ddagger}$ at the coalescence temperature. This is because there is no way of extracting $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ using this method and therefore it cannot be corrected to a standard temperature such as 298 K or the same coalescence temperature of another compound. Because of this, comparisons must be made with care. If $\Delta S^{\ddagger}$ is small, as might be expected in a unimolecular inversion process, then comparisons can be made as the $T\Delta S^{\ddagger}$ term should have a negligible effect on $\Delta G^{\ddagger}$.

Equation 1.1. Rate at coalescence $$k = \frac{\pi}{\sqrt{2}} \upsilon_{AB}$$

Where : k is the rate constant in s^{-1} and υ_{AB} is the separation in Hz of the exchanging signals A and B.

Equation 1.2. $\Delta G^{\ddagger}$ at coalescence $$\Delta G^{\ddagger} = RTc[23 + \ln(\frac{Tc}{\Delta \nu})]$$

Where $\Delta G^{\ddagger}$ is the Gibbs free energy of activation, R is the gas constant, T_c is the coalescence temperature in Kelvin and $\Delta\nu$ is the shift separation in Hz of the fully resolved exchanging signals.

1.1.7.2 Complete Line Shape Fitting

When signals begin to exchange on a time scale similar to that of an NMR experiment, they start to broaden due to Heisenberg uncertainty broadening. The additional broadening of the signals has a direct relationship with the rate of the exchanging spin states. The half height, half width is needed for the calculations, as shown in Equations 1.3 and 1.5, from which the reference broadness is subtracted. This is almost impossible to accurately measure manually from the multiple NMR spectra required. The most reliable technique is to generate spectra based on these parameters until it is possible to map the generated signal onto the real spectra. This is called line shape fitting and the values used to generate the simulated signal can then be used in the relevant equations to extract the activation parameters.

Equation 1.3. Below coalescence $$k = (\Delta v - \Delta_{ref}) \times \pi$$

Equation 1.4. At coalescence $$k = \frac{\pi}{\sqrt{2}} v_{AB}$$

Equation 1.5. Above coalescence $$k = \frac{\pi v_{AB}^{\ 2}}{2(\Delta v - \Delta v_{ref})}$$

Where: k is the rate constant in s^{-1}, Δv peak width at half height of exchanging singlet in Hz, Δv_{ref} peak width at half height of non exchanging singlet in Hz, v_{AB} is the fully resolved peak separation of exchanging signals A and B in Hz.

Importantly, because the fitting can be done over a wide range of temperatures, it is possible to extract $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ using an Eyring plot (Equation 1.6), which can then give $\Delta G^{\ddagger}$ at any temperature (Equation 1.7). The primary benefits of this method are that full activation data can be extracted and, due to the large number of values taken, greater confidence can be placed in the results. As this method is not dependent on the coalescence temperature, it can be used when the coalescence temperature may be partially obscured by similar signals. However, as the position of υ_A and υ_B are still required, sufficient datapoints are still needed in the slow domain to predict their positions at higher temperatures.

Equation 1.6. $$\ln(k/T) = -\frac{\Delta H^{\ddagger}}{R}\frac{1}{T} + \ln\frac{k_B}{h} + \frac{\Delta S^{\ddagger}}{R}$$

$$y = mx + c$$

Equation 1.7. $$\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$$

Where: k is the rate constant in s^{-1}, T is the temperature in Kelvin, k_B is the boltzman constant, h is planks constant, R is the gas constant, $\Delta G^{\ddagger}$ is the Gibbs free energy of activation, $\Delta H^{\ddagger}$ is the enthalpy energy of activation, $\Delta S^{\ddagger}$ is the entropy of activation.

1.1.7.3 EXSY Spectra

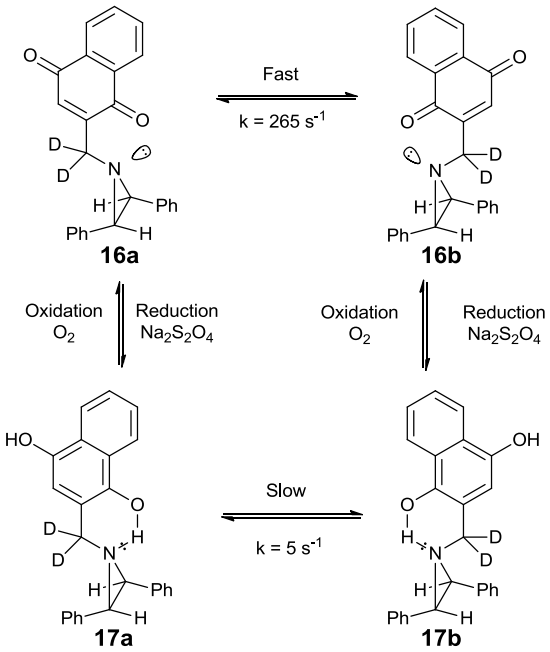
If two NMR signals are undergoing exchange on a time scale similar to T_1 of the NMR experiment, then it is possible to gather quantitative rate data using the EXSY (EXchange SpectroscopY) experiment. One of the signals is selectively saturated and then the spectra observed after the delay period. If the signals are exchanging within this time domain, then enhancement of the other signal is observed. This looks similar to NOE experimental data, however, the physical process is completely different because NOE experiments saturate a signal, which allows T_1 relaxation through dipole – dipole interactions of other hydrogens close in space. In EXSY spectra, it is the excited hydrogen switching spin state during the delay period which causes enhancement. The intensity change, in conjunction with the delay time, allows the rate of the process to be measured. This experiment can be done over a range of temperatures which allows the same thermodynamic data to be obtained as with line shape fitting.

1.1.8 Control of Pyramidal Inversion using Chemical Inputs

Previous research at Warwick has shown that control over nitrogen pyramidal inversion is possible with external chemical inputs, through investigation of a number of aziridine and azetidine based systems. Small nitrogen rings are ideal to study as the ring strain slows the rate of inversion such that it is similar to the NMR time domain. Aziridines and azetidines are also well studied, with a large body of research on which to draw for the synthesis of the target systems.[43,44]

1.1.8.1 Hydrogen Bonding System

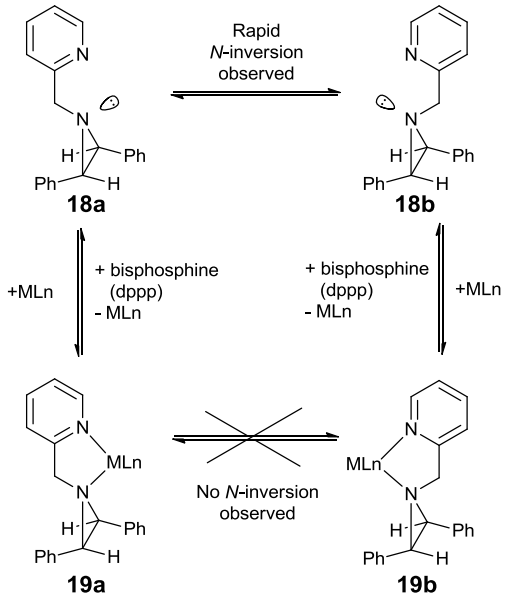
Shipman has previously shown that the rate of inversion can be reversibly controlled by turning a ground state hydrogen bond with the aziridine nitrogen on or off. Naphthoquinone **16** was synthesized and the inversion barrier measured using VT NMR. Reduction to the hydroquinone yielded a hydrogen bond donor in close proximity to the aziridine hydrogen bond acceptor (Scheme 1.4). When the inversion barrier was measured for **17** under the same conditions, the inversion barrier was found to have risen 11 kJ mol^{-1}. This value is in line with the expected strength of a hydrogen bond, reaffirming the assumption that the hydrogen bond must be broken before inversion can occur. This process could be cycled numerous times by mild oxidation and reduction, however the continued addition of chemical reagents eventually caused dilution and degradation. This system allows one to indirectly measure the strength of hydrogen bonds *in situ* and non-destructively.[45]



Scheme 1.4. Redox control of nitrogen pyramidal inversion.[45]

1.1.8.2 Metal Binding System

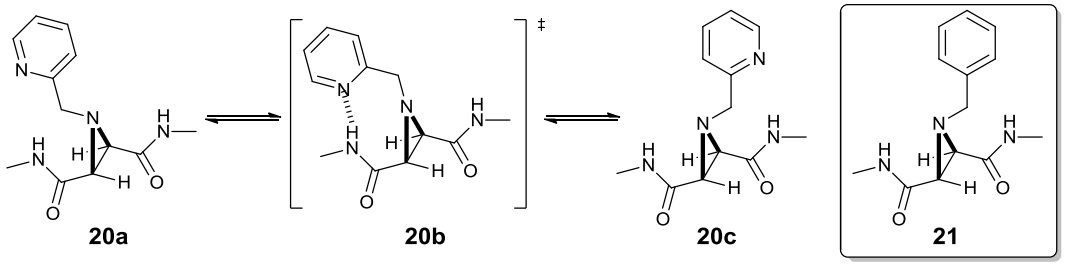
If nitrogen pyramidal inversion could be slowed by a hydrogen bond interaction, then the next logical step was to use a stronger bonding interaction which would completely halt inversion (Scheme 1.5). Compound **18** was developed as a bidentate ligand for metals and a number of metal salts were then screened. $[PdCl_2(MeCN)_2]$ was found to have the strongest interaction. Repeated cycles involving addition of metal and competitive phosphine ligand, allowed the inversion process to be stopped and restarted several times. Again, after a few cycles, the addition of supplementary chemicals caused degradation of the system.[46]



Scheme 1.5. Control of pyramidal inversion using lone pair metal binding.[46]

1.1.8.3 Transition State Hydrogen Bonding

Compound **20** was designed to form a hydrogen bond between the pyridyl hydrogen bond acceptor and the amide hydrogen bond donor. Unexpectedly, the inversion barrier measured was actually lower in the hydrogen bonding system than in a control system **21**, incapable of hydrogen bonding. A double mutant cycle was used to ensure that the structural modifications were not responsible for changes to the inversion barrier. Detailed computational modelling identified that the only viable hydrogen bond was between the amide NH and pyridyl nitrogen. However, this could only occur in the transition state and not in the ground state (Scheme 1.6). This causes stabilization of the transition state relative to the ground state and therefore a reduction in the inversion barrier. This is remarkable as it is one of the few examples of synthesized small molecules which allows for controlled, measurable interactions with a transition state.[47]



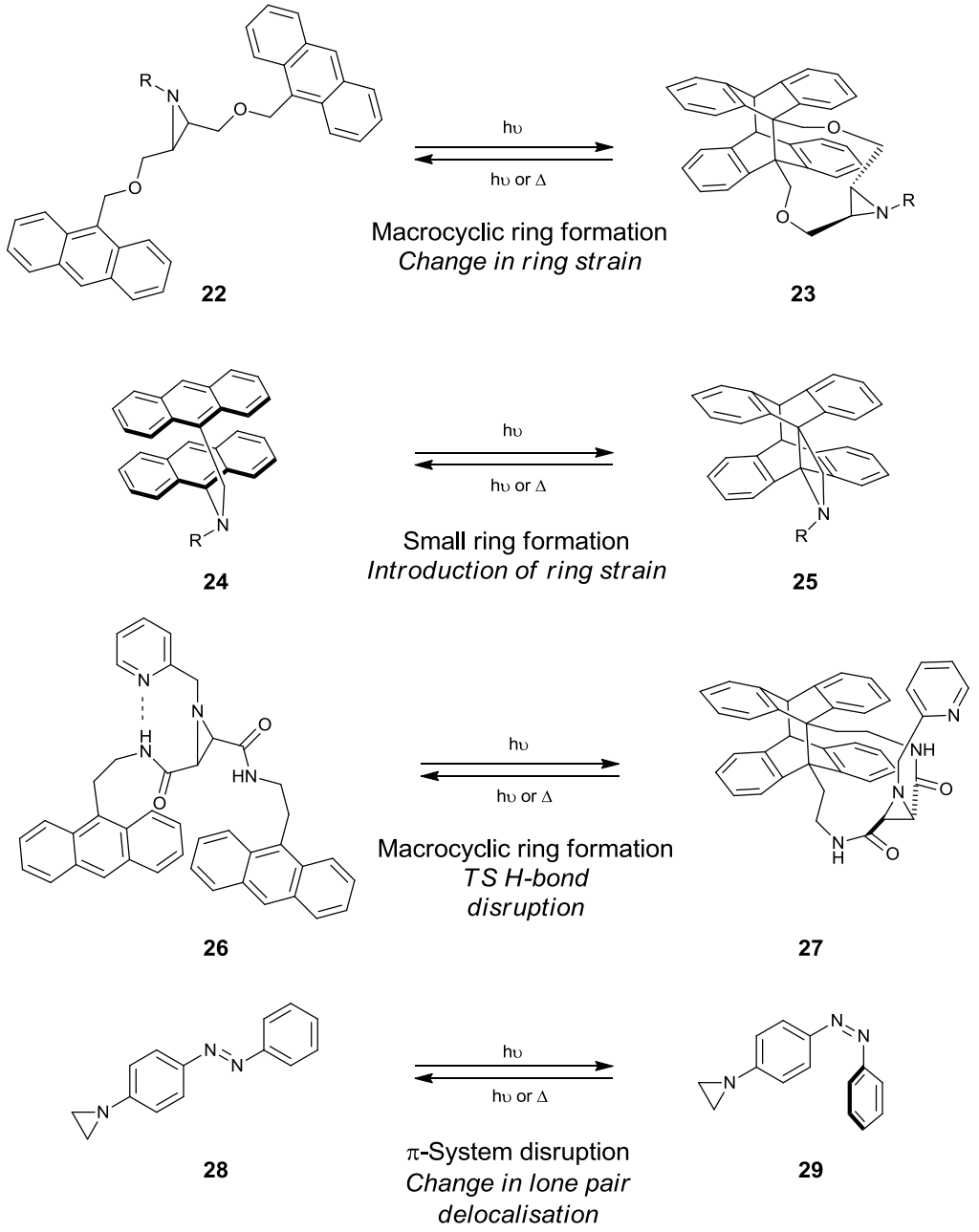
Scheme 1.6. Hydrogen bond only detected in TS by change to inversion barrier and supported by *ab initio* calculations.

1.2 Results and Discussion

1.2.1 Introduction

Small, strained nitrogen rings such as aziridines and azetidines are ideal subjects with which to study nitrogen pyramidal inversion because their inherently high ring strain energy slows the inversion rate sufficiently to be measured by VT-NMR techniques.[46] Our research group has developed a large amount of experience in the organic synthesis and application of complex strained nitrogen ring systems.[48,49] We have previously had success developing systems along these lines where nitrogen inversion can be controlled using chemical inputs.[45-47] Our aim with this project was to extend this knowledge to the design and synthesis of systems which will only require physical inputs such as light and heat to alter rates of pyramidal motion.

To respond to these physical inputs, several design criteria are needed. Firstly, the ability to modify one of the fundamental properties that affect inversion rates, such as angular constraint and orbital hybridization. Secondly, a photochemical "handle" is required which, when activated, will cause a reversible change to the above properties. The systems we chose to study are based on the well-established photodimerisation of anthracene, and separately the photoisomerisation of azobenzenes. Specifically, the heterocyclic systems **22** – **29** (Scheme 1.7) were targeted whose rate of pyramidal motion might respond to light through dimerisation (**22** – **27**) or isomerisation (**28** – **29**). Fuller details of what led to the selection of each system is described in the following sections.



Scheme 1.7. The systems chosen for study.

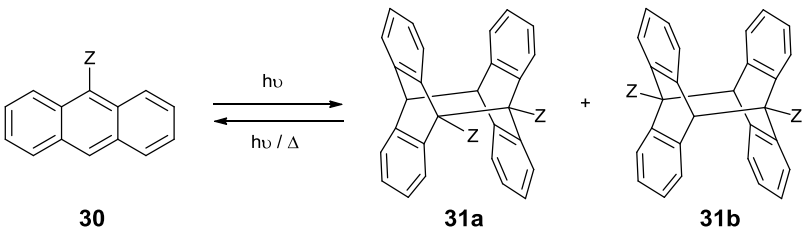
1.2.2 Ring Strain Induced by Macrocycle Formation

We postulated that when a small secondary macrocycle is fused with a nitrogen heterocycle, the degree of angular strain in the heterocycle would increase due to a greater deviation from the ideal bond angles.[50] This small change in ring strain energy was expected to have a significant effect on the rate of pyramidal inversion, as it is extremely sensitive to this parameter.[51]

We were interested in forming a secondary macrocycle on the lower portion of the aziridine ring, between the two carbon substituents. Anthracene has previously been used to photochemically form macrocycles that can be broken by a thermal reverse reaction.[52] Therefore, we decided to incorporate two anthracene moieties into the molecule which would allow control over macrocyclic formation using physical inputs. We focused on the synthesis of compounds related to **22** that fulfil a number of further criteria. The compound is symmetric to ensure equal invertomer populations, which simplifies calculation of the inversion barrier. We chose to use the dimerisation of anthracene as a photochemical means of forming the macrocycle, as the reaction is reversible and it has been successfully applied in similar contexts.[52-54]

1.2.2.1 Anthracene Photochemistry

Anthracene photodimerisation was amongst the first observed photochemical reactions in 1867.[55] It was noted that incident solar radiation on a saturated solution of anthracene in benzene resulted in the formation of microscopic crystals coating the sides of the vessel. The crystals were found to be inert but almost insoluble in organic solvents. Remarkably it was observed that these crystals reverted entirely to their original state thermally (Scheme 1.8). It was later shown that the crystals were an anthracene dimer which did not retain the fluorescent properties of anthracene and was formed by a photoinduced [4π+4π] cycloaddition, which was possible due to the low aromatic nature of the central anthracene ring.[55]

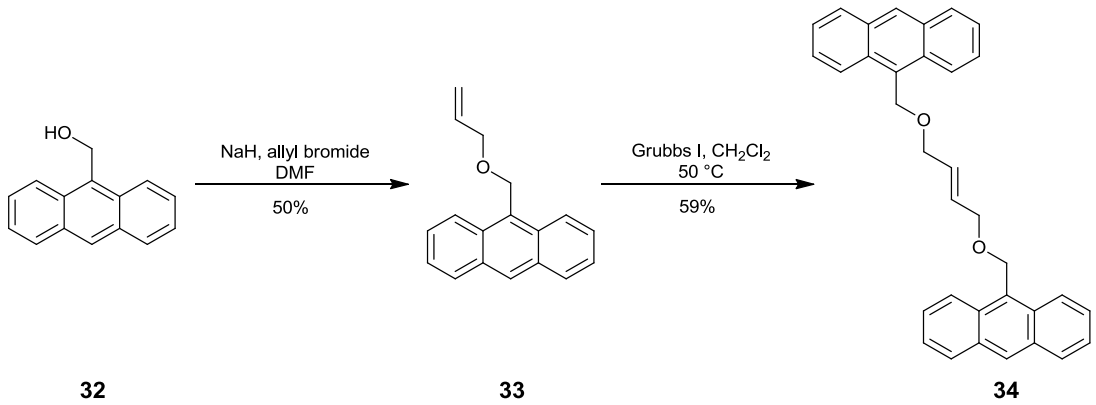


Scheme 1.8. Anthracene dimerization.

The use of anthracene as a photochemical means of controlling molecular and biological properties has been previously demonstrated.[52,54,56] Anthracene would appear to be an ideal photochrome for our studies on pyramidal inversion as its photochemistry has been well studied,[57,58] thus aiding in the design and synthesis of molecules which fulfil our requirements.

*1.2.2.2 Towards the Synthesis of Macrocyclic Precursor **22***

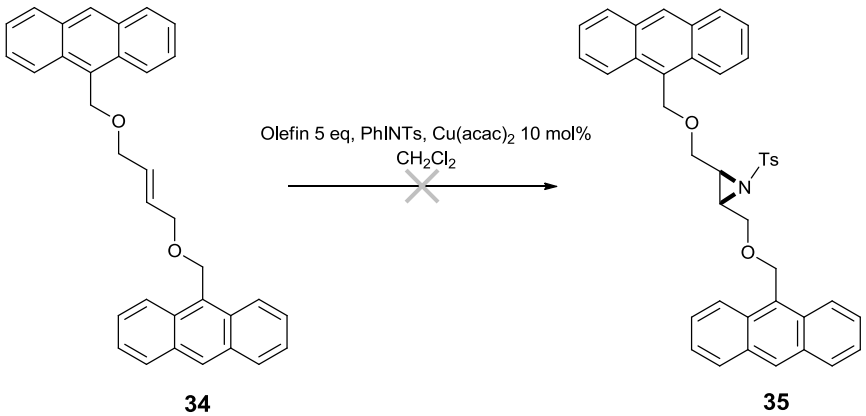
Ether **33** was synthesised using a known procedure[59] and isolated in 50% yield. Dimerisation of this alkene was achieved by intermolecular Grubbs olefin metathesis leading to **34** in 59% yield as an inseperable 3:1 mixture of *trans* and *cis* isomers, the assignment of which was based on comparison to literature ^{1}H NMR values of related compounds (Scheme 1.9). Grubbs first generation catalyst provided a clean reaction, as long as reaction temperatures did not exceed 55 ^{o}C, presumably because higher temperatures can deactivate the catalyst through vessel wall reactions.[60,61]



Scheme 1.9. Synthesis of **34**.

Next, we wanted to undertake direct aziridination of olefin **34**. Metal-catalyzed direct aziridination of alkenes by nitrenes is a reaction that has received a large amount of interest and seemed well-suited to our needs.[62] PhINTs is a well-documented nitrene source,[63,64] which shows high levels of stereoselectivity. Using PhINTs as the nitrene source, it is possible to aziridinate substrates such as styrene and *trans*-stilbene in CH_2Cl_2 under mild conditions.

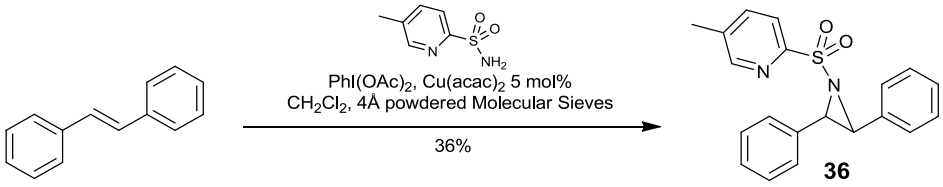
The PhINTs reagent has a number of limitations. It must be prepared, using a low yielding laborious process, immediately prior to the reaction as PhINTs displays poor stability. PhINTs is hard to characterize, so to ensure the synthesised PhINTs was of sufficient quality, concurrent aziridinations of styrene were run as controls. 5 eq of the olefin are typically required and with only limited quantities of **34** available we were unable to fully explore this reaction. However, using reported conditions, the reaction proved unsuccessful (Scheme 1.10).



Scheme 1.10. Attempted aziridination of **34**.

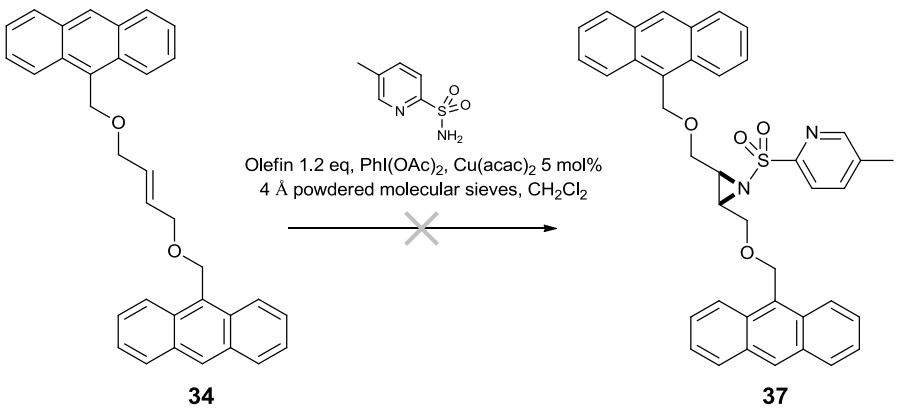
A closely related method has recently been established,[65] which addresses a number of these problems. **36** was successfully synthesised using the reported procedure in

29% yield. Whilst the use of acetonitrile as the solvent worked in this instance, experience has shown that it is ineffective in anthracene systems due to their poor solubility in polar solvents. CH_2Cl_2 has proven to be a good solvent choice for anthracene systems and therefore the reaction was repeated in CH_2Cl_2. Surprisingly, the yield of this reaction was increased to 36%, possibly due to the improved solubility of the aromatic compounds (Scheme 1.11).



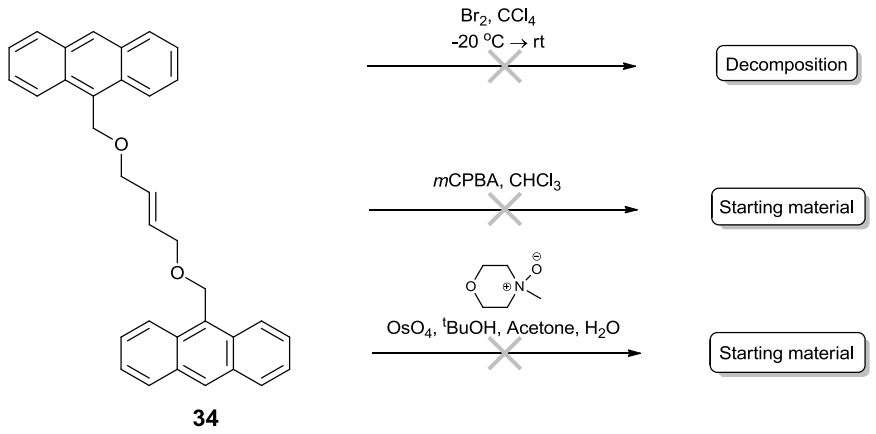
Scheme 1.11. Aziridination of *trans*-stilbene.

Whilst the yield of this transformation is lower than with PhINTs, the nitrenoid is produced *in situ*, removing the need for a separate synthesis. This reaction also only requires 1.2 equivalents of olefin, making it much more appropriate for use within a multi-step synthesis. Olefin **34** was exposed to these modified aziridination conditions in the hope of yielding the *N*-sulfonyl aziridine **37**. Unfortunately, aziridination of **34** using these modified *in situ* conditions were unsuccessful, resulting only in recovery of unreacted starting material.



Scheme 1.12. Attempted aziridination of **34**.

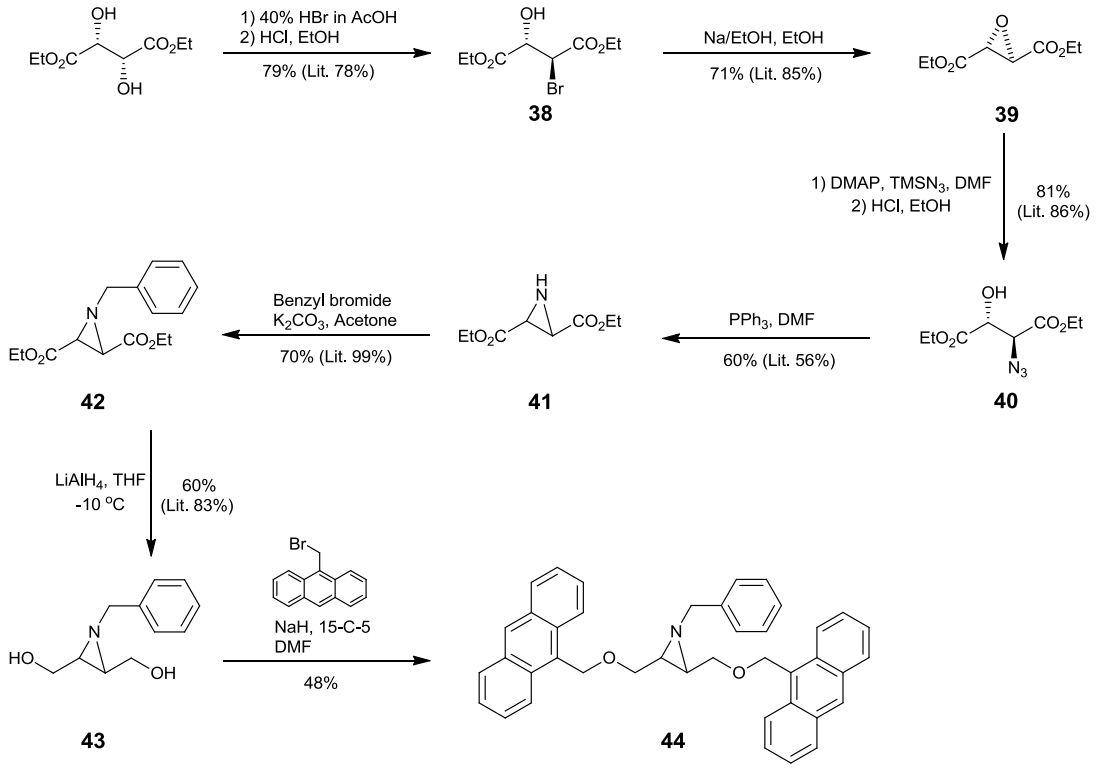
We made further attempts to functionalize the central alkene of **34** using a range of reactions which would introduce functionality that could eventually lead to aziridine ring formation (Scheme 1.13). Attempts to brominate **34** resulted in decomposition with no trace of bromine addition. *m*CPBA epoxidation and Upjohn dihydroxylation were also unsuccessful, with only starting material being recovered.



Scheme 1.13. Attempted functionalization of **34**.

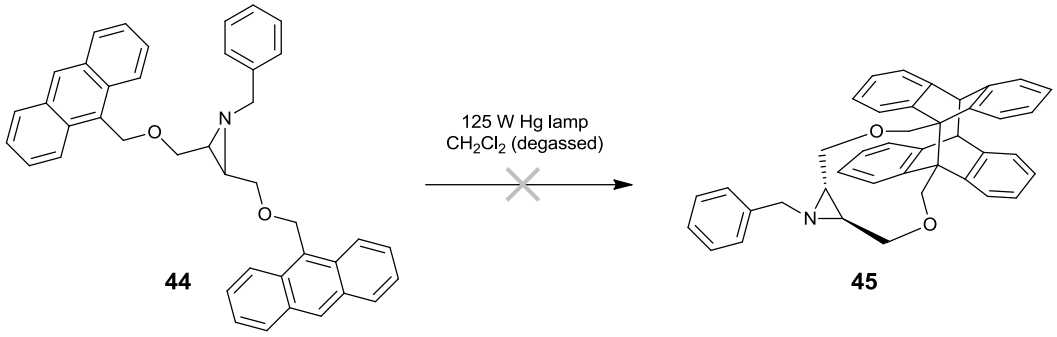
*1.2.2.3 Synthesis of Macrocyclic Precursor **44***

An alternative strategy to **22** was considered. We decided to preform the aziridine nucleus and introduce the anthracene groups later in the synthesis. Using well-documented procedures,[66,67] diol **43** was produced in 6 steps (Scheme 1.14). Treatment of **43** with NaH in DMF, followed by addition of 9-(bromomethyl)anthracene yielded **48** in 48% yield, providing a substrate with which to explore how macrocyclisation might impact pyramidal motion.



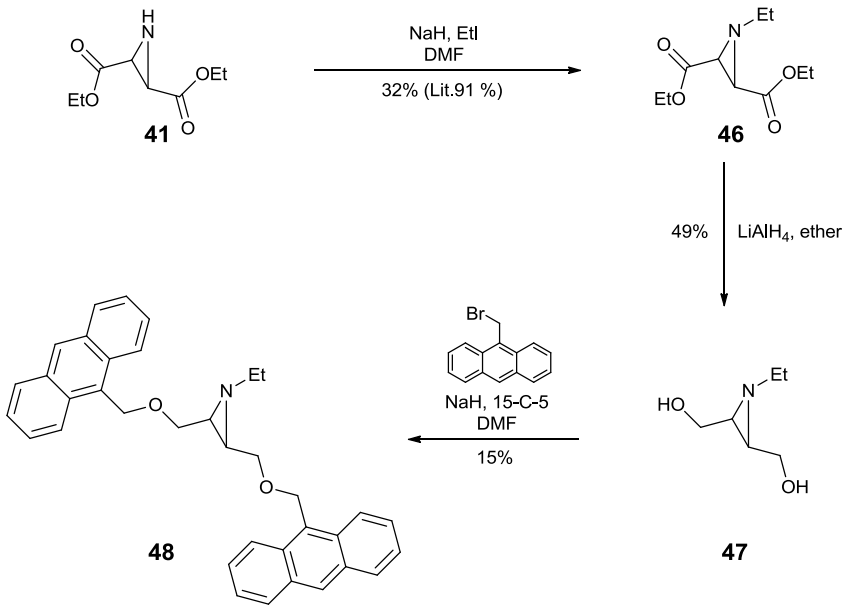
Scheme 1.14. Synthesis of **44**.[66-68]

The photodimerisation of this compound was investigated in collaboration with James Tucker at the University of Birmingham. A small amount of **44** (0.28 μM) in CH_2Cl_2 was extensively degassed by freeze pump thaw cycles under high vacuum. This oxygen-free solution was then irradiated with a 125 W medium pressure Hg lamp through a coated glass band-pass filter centred on 365 nm ± 2 nm (Edmundoptics P/N: NT65-130). A range of reaction times (30 min – 4 h) were investigated, but unfortunately all attempts to photodimerise **44** resulted in degradation (Scheme 1.15). Even though the solvents were extensively degassed, during the longer reaction times, oxidation of the anthracene rings to anthraquinone was observed, along with fragmentation of the compound. This illustrates the sensitivity of anthracene photochemistry to oxidation, and the destructive effect this has on the molecules.[69]



Scheme 1.15. Attempted photoisomerisation of **44**.

We were concerned that the aziridine ring might be the origin of the photochemical instability. To test this idea, aziridine **42** and anthracene were dissolved in benzene. Irradiation under the same conditions used previously, produced anthracene dimer and recovered aziridine **42**, as judged by ^{1}H NMR, indicating that aziridines are stable under these conditions. There are a number of reports[70] to suggest that benzyl groups can cleave and rearrange under high energy UV conditions. Successful alkylation of NH aziridine **41** has been reported only using benzyl bromide and ethyl iodide, with numerous other electrophiles reported to be ineffective.[67] Therefore alkylation of aziridine **41** with ethyl iodide was investigated. Alkylation of **41** with ethyl iodide, freshly filtered through alumina, yielded **46** in 32%. Reduction with lithium aluminium hydride was found to be extremely problematic, with extraction of diol **47** from the aluminium salts formed during the workup proving very difficult. Repeated sonication of these salts with diethyl ether allowed **47** to be extracted, however, the yield remained low (49%).[71] Further alkylation of diol **47** was achieved, providing **48** in a very modest 15% yield (Scheme 1.16).



Scheme 1.16. Synthesis of **48**.

The photochemical experiments were carried out using the same methods as for compound **44** (Scheme 1.15) with the assistance of James Tucker and Luciana Giordano at the University of Birmingham. Disappointingly, degradation of **48** was again seen, even when photoirradiation was limited to 30 minutes. Presumably **44** and **48** are not able to access a conformation where it is possible for the two anthracene rings to align and isomerise to form the macrocycle once in a photoexcited state. This may be because the macrocycle to be formed is rather small. However, if the size of the linking arms was increased to help allow the photochemical reaction to proceed, it is doubtful any significant increase in aziridine ring strain would arise, and hence no detectable change in the nitrogen inversion rate would be observed.

1.2.2.4 Forming Macrocycles via Grubbs Metathesis

The synthesis and purification of the anthracene systems was difficult, primarily because of the poor solubility of the compounds. We wished to verify the effect of macrocycle formation on the rate of pyramidal inversion on a simpler synthetic system. We postulated that the dihedral angle of a *cis* double bond was a good representation of the bridgehead connection of an anthracene dimer (Figure 1.10). Grubbs metathesis was chosen as a reliable synthetic means to form a comparable macrocycle.

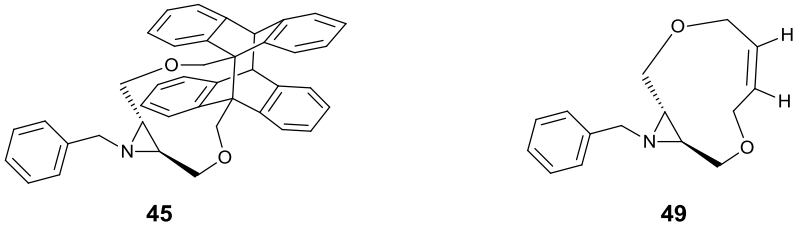
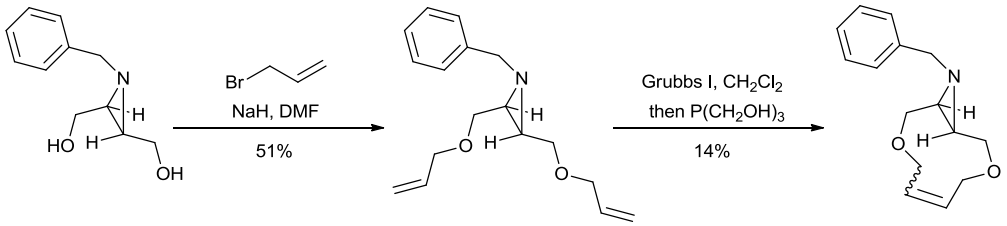


Figure 1.10. Comparison of anthracene (left) and alkene (right) systems.

Treatment of **43** with NaH in DMF, followed by addition of allyl bromide produced **50** in 51% yield (Scheme 1.17). A low concentration of this compound (~2 mM) and 10 mol% Grubbs I catalyst were stirred overnight in dry CH_2Cl_2, however, ESI-MS indicated no product had been formed. An additional 10 mol% of catalyst was added and the reaction heated to 50 ºC to give **51**. This compound was difficult to separate from catalyst decomposition products. Grubbs[72] has reported the removal of spent catalyst *via* a water soluble tridentate phosphine, $P(CH_2OH)_3$.

The reaction was repeated and the ligand was prepared[73] then used as described, by addition of 20-30 eq of ligand in IPA relative to catalyst, following the metathesis reaction. After an aqueous work-up this reaction mixture was more easily purified to

give **51** in 14% yield, consisting of an inseparable mixture of both geometric isomers in an approximately 7 : 3 ratio (*trans* : *cis*). Ideally, the *cis* isomer was desired to emulate the anthracene bridgehead. However, comparison with literature ^{1}H NMR shifts of similar products[74] and the usual Grubbs I ratio indicated the major product was most likely the *trans* isomer.[75] Unfortunately, the product was not very stable and decomposed during further NMR experiments to confirm this assumption.



43 **50** **51**

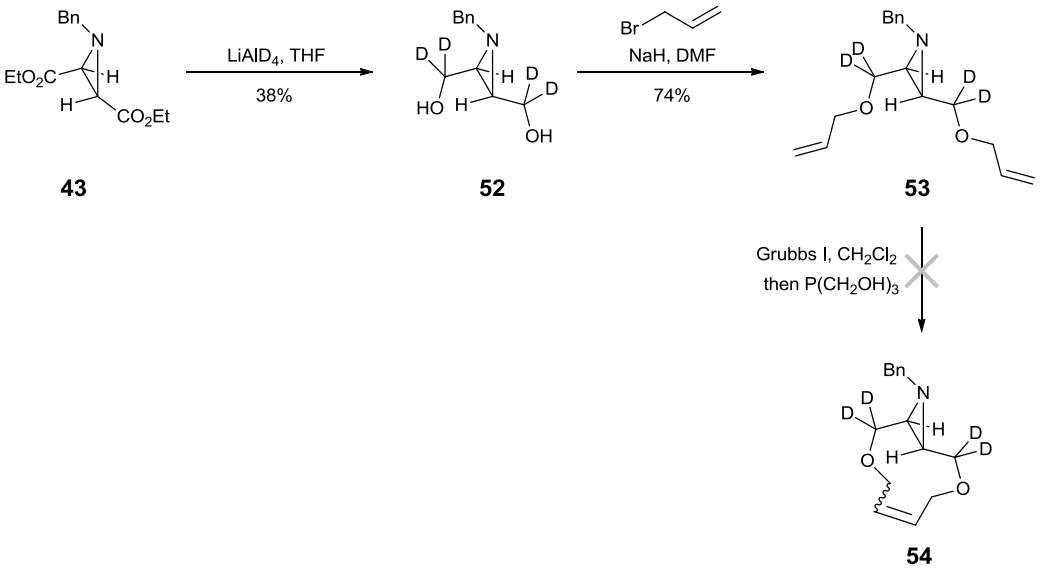
Scheme 1.17. Synthesis of **51** *via* Grubbs metathesis.

It was expected that Grubbs II catalyst might be a more appropriate catalyst, leading to improved yields of alkene **51**.[76] However, attempts using this catalyst led only to recovery of starting material.

Further problems were encountered when VT-NMR spectra were recorded using **51**. The aziridine hydrogens, from which the inversion barrier is calculated, were coupled to the adjacent methylene hydrogens, making the spin system too complex for coalescence temperature calculations[33] or line shape analysis using WinDNMR.[77] Data that was collected using approximate T_c calculations based on the coupled ^{1}H shifts (**50**, T_c = 358 K, $\Delta G^{\ddagger}$ = 71.1 kJ mol^{-1}; **51**, T_c = 338 K, $\Delta G^{\ddagger}$ = 67.8 kJ mol^{-1}), indicated that there may indeed be a difference in the rate of pyramidal inversion, but in the opposite direction to that anticipated. The original hypothesis was that increasing the angular constraint by forming a fused ring system would raise the

barrier, but this data suggests that ring closure may destabilise the ground state, possibly by steric interactions.

In order to obtain better quality data, we decided to synthesise d_4-**50**, which would have a simple AB aziridine spin system (Scheme 1.18). Reduction of **43** with lithium aluminium deuteride yielded diol **52** in 38% yield with 99% deuterium incorporation as determined by ^{1}H NMR. Encouragingly, the ^{1}H NMR spectrum showed the aziridine hydrogens to be a simple uncoupled AB system. Diol **52** was allylated to give **53** in 74% yield. Unfortunately, ring closing metathesis using deuterated **53** did not lead to macrocycle **54** despite several attempts. Repeating of the Grubbs reaction for the initial *bis*-alkene **50** also failed to give consistent results. Indeed, this metathesis reaction proved to be very unreliable, most likely due to the difficulty of forming a strained ring *via* ring closing metathesis.



Scheme 1.18. Attempted synthetic route towards **54**.

1.2.2.5 Conclusions

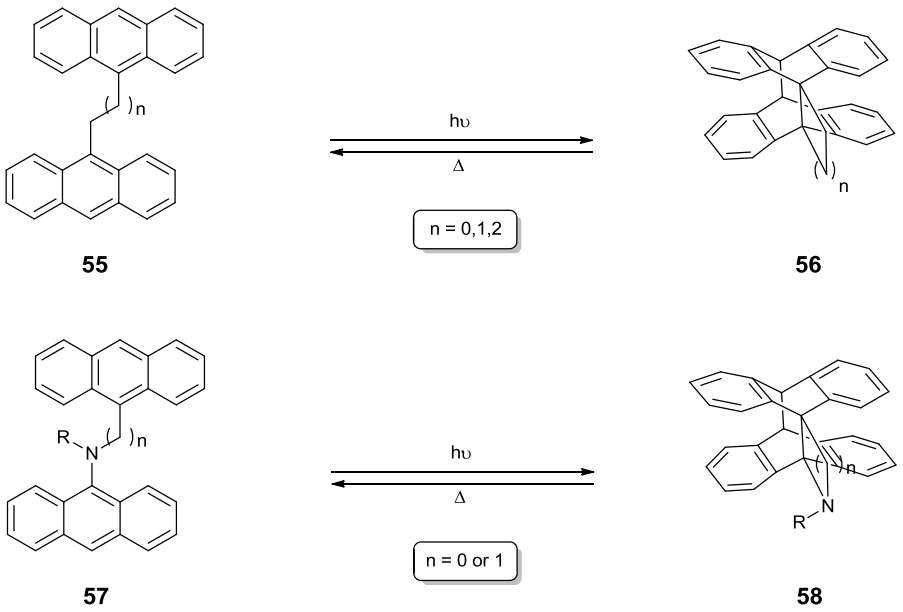
The synthesis of *bis*-anthracene containing aziridines **44** and **48** was achieved in 7 steps in acceptable yields. We were able to demonstrate that aziridine **42** is stable to anthracene photochemical conditions, but we were unable to photoisomerise *bis*-anthryl aziridines **44** and **48** to macrocycles.

To model their behaviour, diene **50** was made in 7 steps and its ring closing metathesis to **51** achieved. There is some indication from T_c calculations that this ring closure produces a change in the inversion barrier. However, the unreliability of this reaction, and the failure with the photochemical reactions led us to abandon this avenue of research.

1.2.3 Ring Strain Induced by Small Ring Formation

1.2.3.1 Introduction

To maximise the probability of successful photochemistry with our systems, we moved towards simplified structures that were closely related to carbocyclic systems already established to undergo photodimerisation. Specifically, Bergmark[78] has shown that **55** can be reversibly transformed into **56**, containing 3 – 5 membered carbocycles (Scheme 1.19).[58] The photochemistry of these carbocyclic compounds is reported to be very efficient due to the anthracene rings being held in close proximity, although in the case of the one carbon linker, the cyclisation is postulated to proceed in a stepwise process rather than a single concerted step due to the differing planes of the anthracene rings.[58]



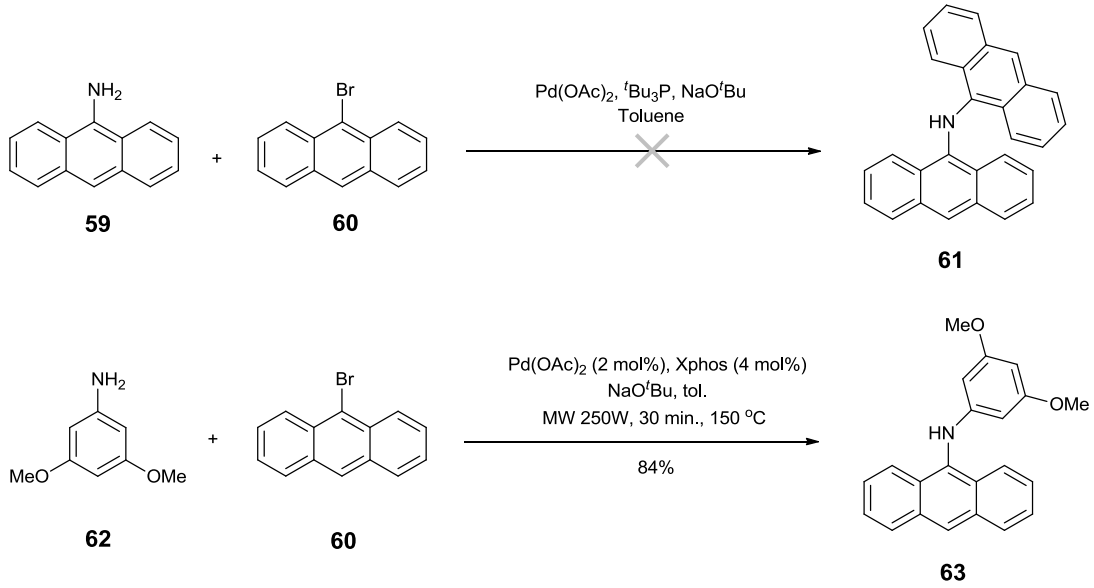
Scheme 1.19. *Bis*-anthryl amine based systems related to known carbocyclic systems.[58]

In an analogous manner, we envisaged that **57** could be photoisomerised to aziridine or azetidine containing **58**. Large changes in *N*-inversion barriers would be expected between **57** and **58** as a result of introduction of ring strain.

*1.2.3.2 Synthesis of Bis Anthryl Amines **61, 68** and **70***

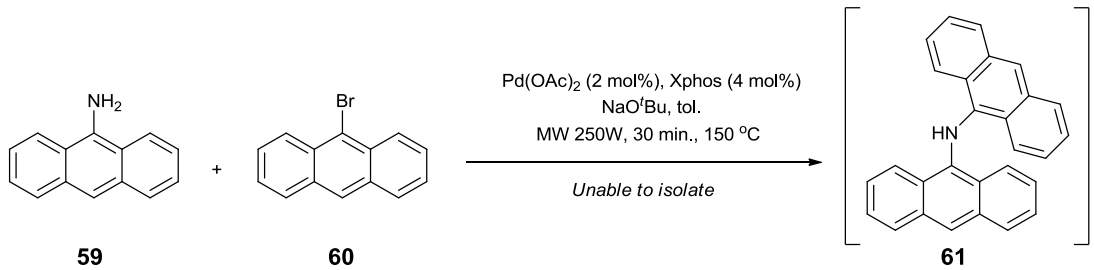
Our initial attempts focused on an amine linker which, upon dimerisation, would yield aziridine **58** (n = 0). We attempted a Buchwald amination[79] of 9-aminoanthracene **59** with 9-bromoanthracene **60**. 9-Aminoanthracene was easily prepared using reported methods,[80] but unfortunately early attempts were hindered by the difficulty in following the reaction by ^{1}H NMR spectroscopy and were unsuccessful using Fu's highly reactive tri-*tert*-butylphosphine ligand. To make reaction analysis easier, a range of published Buchwald conditions were applied to a model system involving the use of amine **62** (Scheme 1.20).[79] In this way, we

identified xphos as the preferred ligand and NaO^{t}Bu as the best base for the synthesis of **63**.



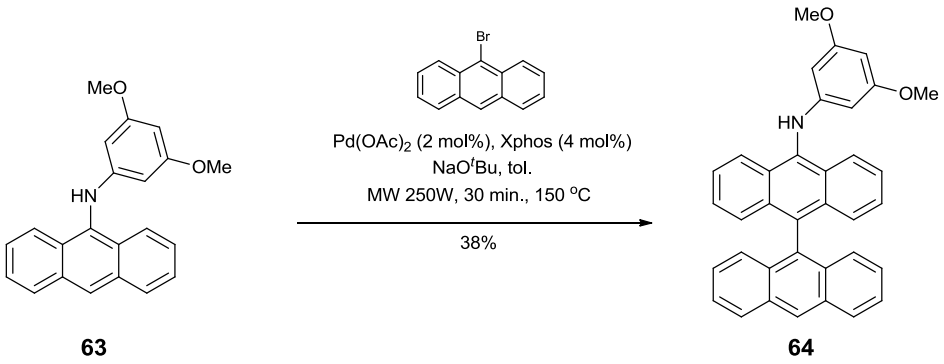
Scheme 1.20. Buchwald amination.

Once the conditions had been optimised, they were then applied to the *bis*-anthryl system (Scheme 1.21). The reaction did not proceed as cleanly as the model reaction, but the product was clearly visible by ESI-MS and ^{1}H NMR. Disappointingly, attempts to isolate **61** by chromatography using silica gel or alumina, or by crystallisation as either the free base or as the corresponding hydrochloride salt, were unsuccessful. Attempts were also made to alkylate the crude product with methyl iodide or tosyl chloride, neither of which gave any indication of the desired products.



Scheme 1.21. Optimised Buchwald amination conditions applied to the synthesis of **61**.

Attempts to undertake a second Buchwald amination on **63** led to the unexpected formation of **64** (Scheme 1.22). This was indicated by the ^{1}H NMR signal (δ = 8.69 ppm) corresponding to the H-10 anthracene integrating to one hydrogen, and a lack of equivalence in the remaining anthracene signals. This gave an insight into the reactivity of these compounds, which was further confirmed by the attempted methylation of **59** and **61**, which rapidly underwent multiple methylations (up to four) by mass spectrometry. In general, all of the unsubstituted aminoanthracenes prepared showed poor stability and even 9-aminoanthracene itself oxidises and degrades rapidly in solution.

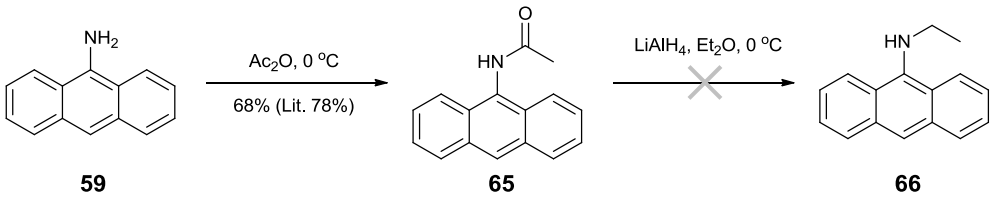


63 **64**

Scheme 1.22. Unexpected formation of **64** under Buchwald amination conditions.

9-Aminoanthracenes are rare, however, *N*-acetylaminoanthracene is a well-known compound.[81] This was prepared according to the literature method, in the hope that it could be reduced with lithium aluminium hydride, to form *N*-ethyl aminoanthracene. The stability of *N*-ethyl aminoanthracene was again found to be poor, however, the observed stability of the *N*-acetyl aminoanthracene compared to the parent aminoanthracene was interesting. Unfortunately *N*-carbonyl aziridines are not useful for this project, as the strong overlap of the nitrogen lone pair into the carbonyl system causes the ground state to be planar or near planar, therefore exhibiting very

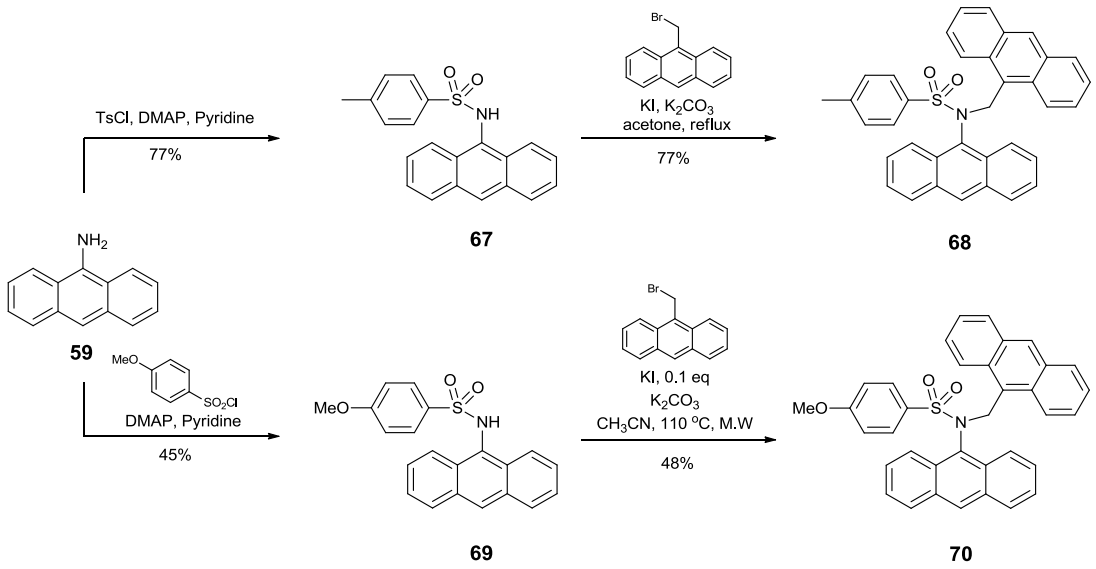
little pyramidal character. The stability of **65** is presumably due to some degree of delocalisation of the nitrogen lone pair away from the anthracene ring system.



59 **65** **66**

Scheme 1.23. Acetylation of 9-aminoanthracene.[81]

Based on these observations, we decided to target *N*-sulfonyl amines which we hoped would yield stable compounds yet retain some pyramidal character. Unfortunately, it was anticipated that aziridine systems could only be readily synthesised using Buchwald amination reactions, which are unsuitable for producing *N*-sulfonyl amine linked anthracenes. Thus, we decided to target the related azetidine precursors (**68** and **70**), allowing different synthetic routes to be employed. Tosylation of **59** was achieved using standard conditions yielding **67** (Scheme 1.24), which had only been reported previously as a photochemical side product.[82] Using catalytic potassium iodide and potassium carbonate in acetone, and heating to reflux for two days with bromomethyl anthracene, *bis*-anthracene **68** was obtained in a pleasing 77% yield. Using the same procedure, **70** was also synthesised using 4-methoxybenzenesulfonyl chloride as the electrophile to form sulfonamide **69** in 45% yield. Alkylation was explored under microwave conditions (300 W, 110 °C, 15 min.). The yield of 48% is lower than the thermal conditions used for **68**, but the reaction time is much shorter. The intention of adding the *p*-methoxy group was to improve solubility, which was causing difficulty when purifying by chromatography. However, there was no noticeable difference in the solubility of **68** and **70**.



Scheme 1.24. The synthesis of **68** and **70**.

A suitable crystal for X-ray analysis of **68** was grown using the solvent diffusion method from dichloromethane and diethyl ether. This not only revealed the near planar nature of the nitrogen substituents ($\Phi = 162^{o}$, measured as the angle of the N – R_3 plane relative to the R_1 – N – R_2 plane) in this compound, but also how well the anthracene rings were set for dimerisation, being only 2.8 Å apart. The barely pyramidal nature of the nitrogen centre is disappointing, as any inversion process would be extremely rapid and very difficult to measure.

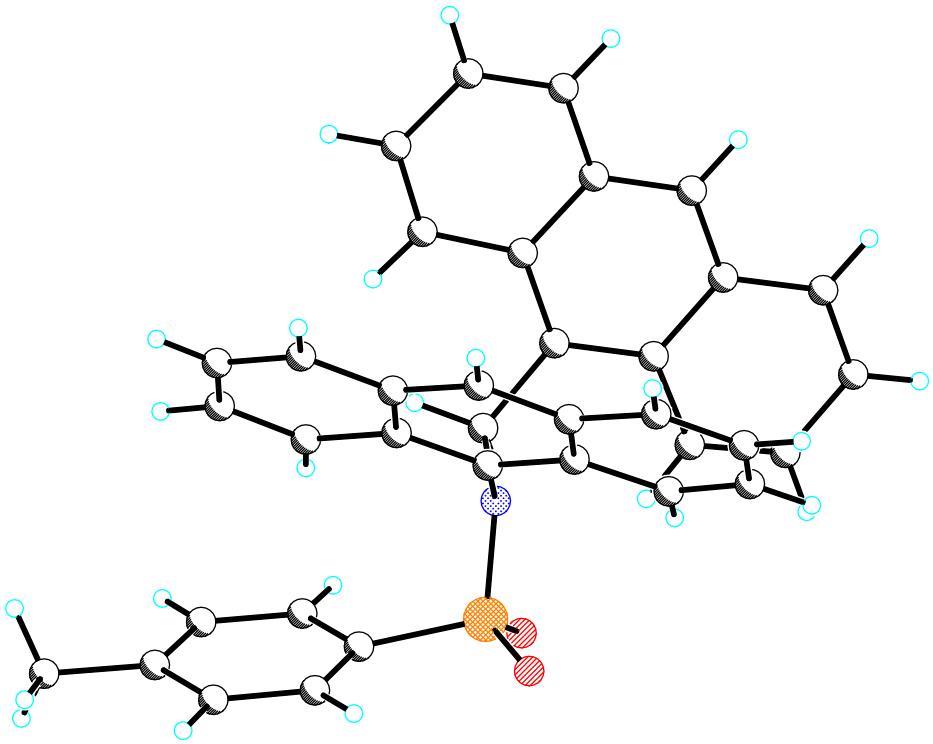
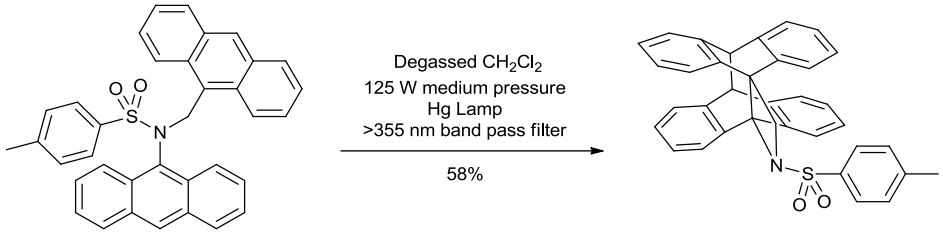


Figure 1.11. X-ray crystal structure of **68**.

*1.2.3.3 Photoisomerisation of **68***

The photochemistry of **68** was initially investigated at the University of Birmingham with the assistance of James Tucker and Luciana Giordano. Irradiation of **68** (1.86 μM in degassed CH_2Cl_2) using a 125 W medium pressure Hg lamp through a glass bandpass filter centred on 365 nm ± 2 nm (Edmundoptics P/N: NT65-130) for one hour, yielded photodimer **71** in an encouraging 58% yield. The ring closure was supported by the appearance of two strongly coupled AB doublets at 4.5 ppm in the ^{1}H NMR, and no change in molecular ion mass indicated that intramolecular isomerisation was occurring.



68 **71**

Scheme 1.25. Irradiation of **68** to form **71**.

Low temperature VT-NMR data for **71** was collected in d_2-dichloromethane. A coalescence temperature of –80 ^{o}C was measured but, unfortunately, the freezing point of dichloromethane is at –95 ^{o}C and the operational limit of a standard NMR probe is –100 ^{o}C. Because of this, it was not possible to obtain sufficient data in the slow inversion regime to determine the maximum separation of the resolved signals. Hence, complete line shape analysis was not possible as the true position of υ_A and υ_B could not be plotted. However, using the Equation 1.7 it was possible to estimate ΔG for **71** at coalescence, $\Delta G^{\ddagger}$ = 35 kJ mol^{-1} at 193 K. This is higher than that reported for *N*-tosyl azetidine, which has a reported inversion barrier of 26 kJ mol^{-1} at 123 K in $CHClF_2$.[33]

Equation 1.7. $\Delta G^{\ddagger}$ at coalescence. $$\Delta G^{\ddagger} = RTc[23 + \ln(\frac{Tc}{\Delta \nu})]$$

One might expect a decrease in the inversion barrier rather than the increase observed due to the large number of steric interactions in **71** in the ground state when compared with *N*-tosyl azetidine. Such interactions would be expected to destabilize the ground state relative to the transition state thereby reducing the required energy to progress from the ground to the transition state. Presumably **71** has increased ring strain compared with *N*-tosyl azetidine.

1.2.3.4 Conclusions

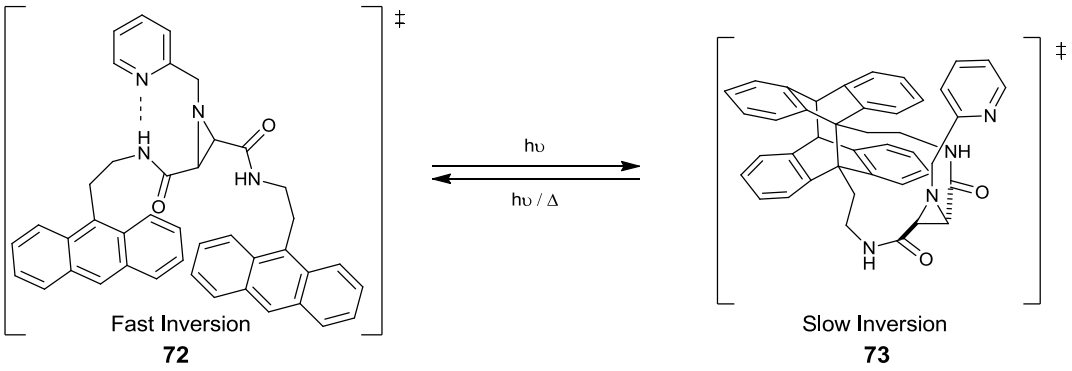
Although our efforts towards the synthesis of the aziridine family were unsuccessful due to poor stability, we were able to successfully synthesise members of the *N*-sulfonyl azetidine family. Azetidine **71** was synthesised in five high yielding steps, which included an efficient anthracene photoisomerisation. Unfortunately, the crystal structure of **68** showed it was very close to being planar at the nitrogen centre, and had very little pyramidal character. The pyramidal inversion of **71** was fast enough to be at the limit of VT-NMR investigation, however we were able to calculate activation parameters through coalescence. This azetidine proved to have a higher pyramidal inversion barrier than *N*-tosyl azetidine, an observation that merits further investigation by computational modeling.

This system did not possess all the ideal attributes to allow us to demonstrate photocontrol of pyramidal inversion and hence we decided to examine alternate systems. However, because the photochemical isomerization in these molecules was found to be very efficient, we went forward to modify these systems to form light-activated β-lactam antimicrobial agents. This subject is discussed in detail throughout Chapter 2.

1.2.4 Using Light to Disrupt Hydrogen Bonds

1.2.4.1 Introduction

Shipman has shown that hydrogen bonds can be used to modify the rate of pyramidal inversion. In 2006, ground state hydrogen bonds were used to slow pyramidal motion.[46] More recently, transition state stabilising hydrogen bonds were used to accelerate *N*-inversion (Schemes 1.4 – 1.6).[47] We wanted to combine this established hydrogen bonding aziridine fragment with the ability to form a large macrocycle through photochemistry. In this way, the hydrogen bond could be disrupted by macrocycle formation. We chose to attempt this using *bis*-anthracene so that this process could be controlled using light / heat.

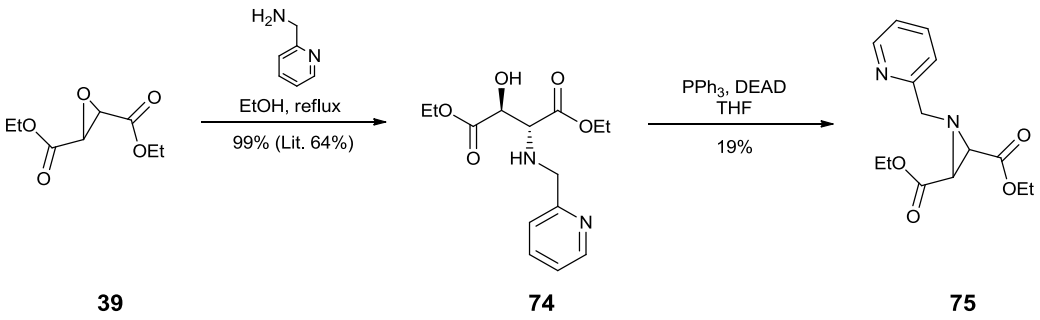


Scheme 1.26. Control of inversion *via* macrocycle formation to disrupt hydrogen bonding.

*1.2.4.2 Towards the Synthesis of Precursor **72***

Aziridine **75** was synthesised in 2 steps from epoxide **39** (Scheme 1.27). Initial ring opening with 2-picolylamine occurred in a 99% yield. Ring closure of **74**, under standard Mitsunobu conditions using DEAD, was achieved with difficulty and problems were encountered in isolating **75** from the reduced DEAD (EtO_2CNH-

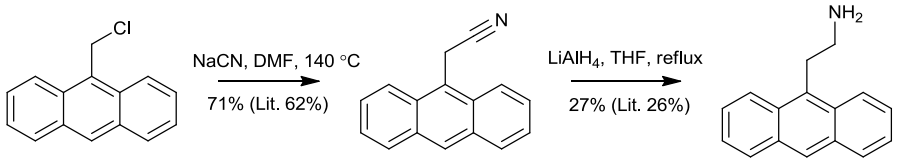
$NHCO_2Et$). A low yield of 19% was obtained, which still contained some minor contaminants.



39 **74** **75**

Scheme 1.27. Synthesis of aziridine **75**.[47]

Anthryl amine **78** was synthesised *via* nitrile **77** (Scheme 1.28). Commercial 9-chloromethyl anthracene **76** was treated with sodium cyanide at 140 ^oC to give **77** in 71% yield. Reduction of nitrile **77** using lithium aluminium hydride under forcing conditions produced a mixture of compounds with **78** being isolated in just 27% yield. Large quantities of sodium cyanide must be used in order to produce usable amounts of amine **78** and, additionally, both compounds are very insoluble, therefore making isolation difficult.



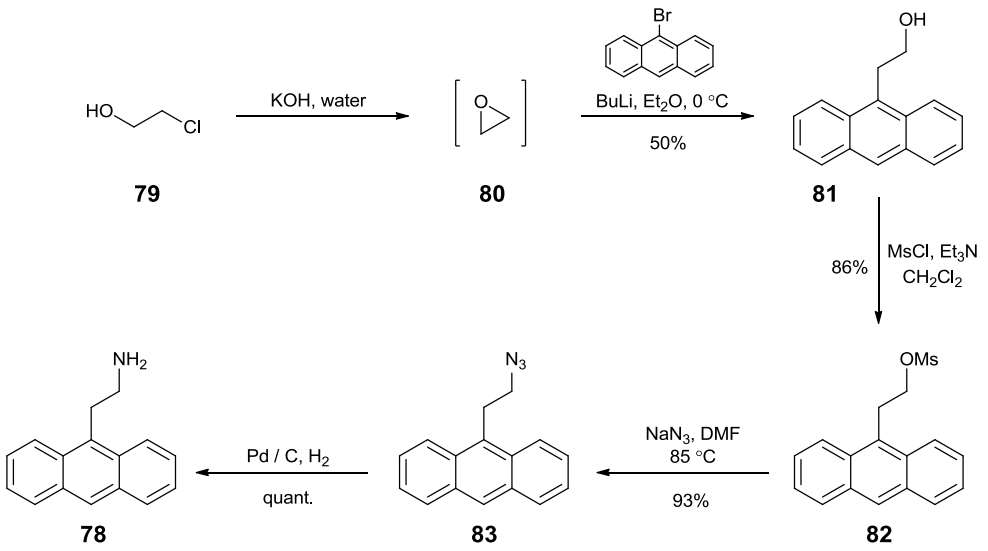
76 **77** **78**

Scheme 1.28 Reported synthesis of amine **78**.[83]

In order to safely and effectively produce sufficient amine, a new route was required, which is shown in Scheme 1.29**.** It has previously been shown that lithiated 9-bromoanthracene can effectively ring open oxirane to yield alcohol **81**.[84] Commercial oxirane is expensive due to the cost of containment, but can be easily

prepared, although it does require special precautions due to its toxicity. 9-Bromoanthracene was lithiated using *n*-butyllithium at −78 °C, then warmed to 0 °C and reacted with excess oxirane to give alcohol **81** in 50% yield.

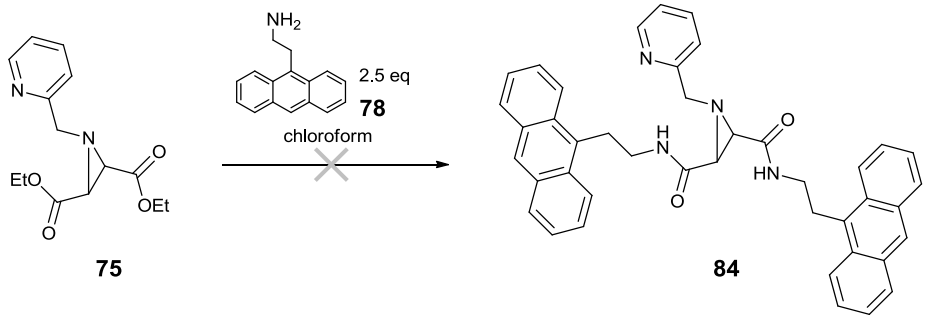
Mesylation of **81** was achieved using standard conditions in 86% yield, followed by substitution with a sodium azide in 93% yield. Final reduction of azide **83** using hydrogenation catalyzed by palladium on activated carbon was quantitative. This new route employs a greater number of steps, but each of the steps are easier to accomplish, especially in terms of purification and can be more readily scaled up.



Scheme 1.29. Improved synthetic route towards amine **78**.

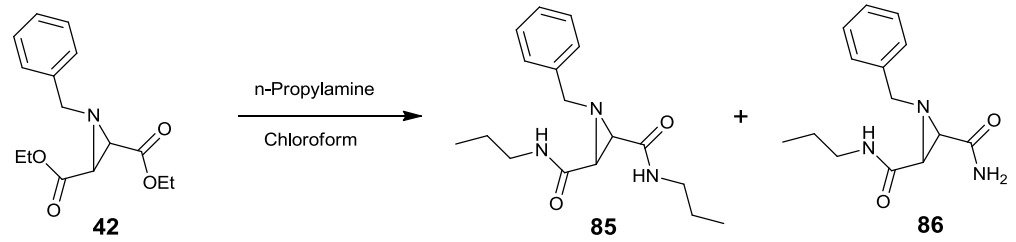
With the required amine in hand, attempts were made to react it with aziridine **75** (Scheme 1.30). Previously, this substrate had been reacted with a large excess of methylamine (20 eq) in methanol.[47] However, because of the limited availability and solubility of **78**, we attempted the reaction using 2.5 eq of **78**. After 1 week, there was no indication of any conversion to amide **84**. In the initial research for this reaction no attempts were made to optimize the reaction conditions as methylamine

is highly soluble and was used in a large excess as a solution in methanol with chloroform as co-solvent.[47]



Scheme 1.30. Attempted amide formation.

As pyridine **75** and amine **78** were in short supply, a model reaction was investigated. *n*-Propylamine was chosen as the amine and aziridine **42** was used in place of **75** as it is much easier to make (Scheme 1.31). The reaction was conducted with 5, 10, 20 and 40 eq of amine in an 0.18 M solution of aziridine using chloroform as the solvent. The 40 eq reaction was found to be complete within 2 days, whereas the 20 eq reaction required 5 days. The 10 eq reaction was much slower and, after 1 week, there was mainly starting material (62%), monosubstituted product **86** (38%) and trace amounts of the required di-substituted product **85**. The 5 eq reaction showed no indication of any conversion after 1 week, which supports the earlier disappointing result obtained using the anthryl amine **78** (Scheme 1.30).



Scheme 1.31. Optimization of amide formation.

Further attempts were made using the anthryl ethylamine **78**, however, when the quantity of this compound was increased, it was found to not fully dissolve in the available solvent. The maximum that was possible to dissolve was about 5 eq, which is far from the ideal 20 eq required for the reaction, and therefore it was not possible to drive this amidation reaction to completion.

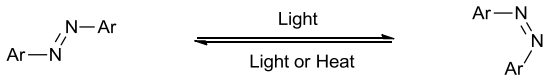
1.2.4.3 Conclusions

Unfortunately, our efforts to make **72** were primarily thwarted by the poor solubility of the anthracene derivatives. The key amide forming step of this synthesis requires a high concentration of amine in order to force the reaction to completion, but it was not possible to obtain these high concentrations using anthryl ethylamine **78**. Alternative amide coupling reactions were briefly explored, however, they were unsuccessful and limited by the presence of the aziridine ring. On the positive side, an improved synthesis of **78** has been developed compared to literature methods as well as optimization of the amide forming step using *n*-propylamine.

1.2.5 Azobenzene Photoisomerisation Based Systems

1.2.5.1 Introduction

Azobenzenes have been widely used in rotaxane and catenane chemistry to make photoresponsive systems.[85] They have also been widely used in molecular rotors and meshed gear systems,[86] and to control biological processes.[87] The photochemistry of azobenzenes is well understood,[88,89] and the interconversion of the *cis* to *trans* isomers can be achieved in high conversion and cycled many times without significant degradation (Scheme 1.32). The synthesis of such molecules is also well-documented due to their extensive use as dyes.[90]

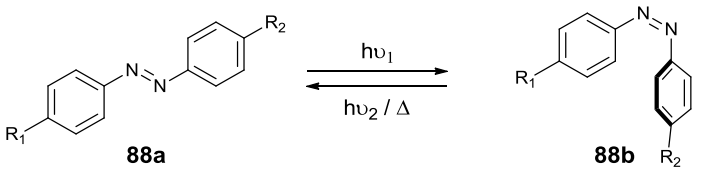


trans- **87** *cis*- **87**

Scheme 1.32. Isomerisation of azobenzenes.

Trans azobenzenes **88a** are completely planar with extensive delocalization throughout the ring system.[91] For azobenzene, irradiation causing a symmetry allowed $\pi \rightarrow \pi^*$ transition (λ_{max} = 320 nm) or a very weak unresolved $n \rightarrow \pi^*$ transition (λ_{max} = 450 nm), causes an isomerisation of the azo bond to occur, forming *cis* azobenzene **88b**. Two mechanistic pathways have been reported for the isomerisation. Firstly, rupture of the N=N π bond followed by either rotation or, alternatively, inversion of one nitrogen centre, leads to the *cis*-isomer. It is likely a combination of both the bond rotation and inversion pathways that is responsible for isomerisation in most cases.[88] Due to steric interactions, it is necessary for one of the aromatic rings to twist out of the plane, reducing conjugation in the *cis* product.[92,93] This twist restricts the aromatic orbital overlap and therefore the degree of

conjugation between the two rings. The *cis* isomer can be converted back to the *trans* isomer by irradiation. For azobenzene, the *cis* $\pi \rightarrow \pi^*$ transition (λ_{max} = 270 nm) is weaker but the $n \rightarrow \pi^*$ transition (λ_{max} = 450 nm) absorbs much more strongly than the *trans* isomer. There is also a thermal pathway from the *cis* isomer towards the thermodynamically more stable *trans* isomer, the barrier to which is dependent on the aromatic substituents.



Scheme 1.33. Conversion of azobenzene *cis* and *trans* isomers.

We hypothesised that the different electronic structures of the *cis* and *trans* azobenzene isomers could be used to modify the rate of pyramidal inversion. We have described earlier how sensitive the rate of inversion can be to the p character of the nitrogen lone pair, which is influenced by the nature of any adjacent π systems. Andose[41] has compiled data that shows there is approximately a difference of 12.5 kJ mol^{-1} in $\Delta G^{\ddagger}$ between the inversion energies of *N*-phenyl and *N*-*p*-nitro phenyl aziridines (Figure 1.12).

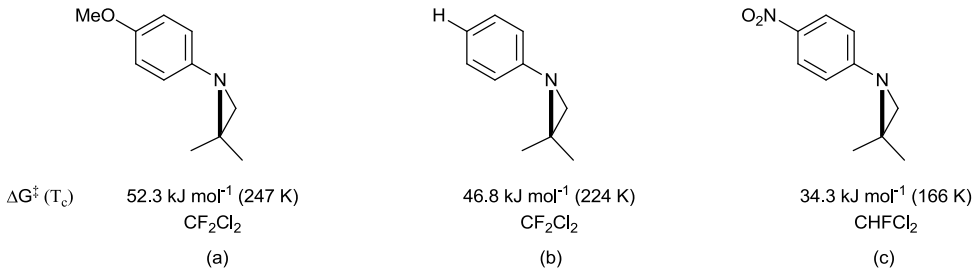


Figure 1.12. Inversion barrier of aryl aziridines from line shape fitting (a & b) and T_c calculations (c).[41]

Based on this evidence, it seemed reasonable to propose that azobenzene isomerisation could significantly alter the nature of an attached *N*-aryl π-system, and have a measurable effect on the inversion parameter. We selected aziridines **89** and **90** as suitable systems to test these ideas (Figure 1.13). For VT-NMR analysis, **89** is most attractive as the aziridine hydrogens are a simple AB system. However, synthetically, **90** appeared most attractive, especially as it has been made previously by Hallas.[94]

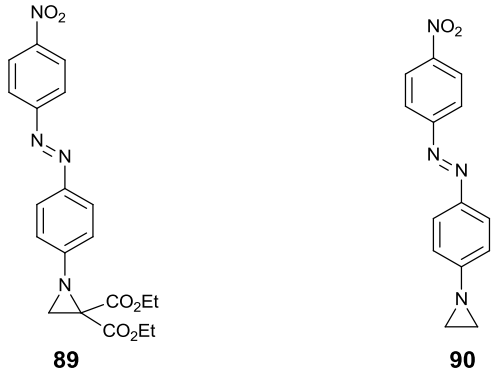


Figure 1.13. Aziridine targets **89** and **90**.

For this work, we restricted ourselves to aziridine based systems. This is because reported values for analogous phenyl and *p*-NO_2 phenyl azetidines, place the inversion rate beyond the limits of study by VT-NMR spectroscopy.[33] It is known that azobenzenes with appended *N*-heterocycles of four membered rings and higher

are planar, whereas aziridine rings were determined to be mainly tetrahedral at the nitrogen centre.[95] Research by Hallas *et al*[94,96] has, for a number of years, focused on the construction of azobenzenes functionalized with small, strained terminal nitrogen rings intended as modified azo dyes. It was expected, and demonstrated in a series of papers,[97,98] that with adequate ring strain it was possible to forcibly alter the orbital character of the terminal nitrogen, which in turn affected the electronic structure of the azobenzene due to differing orbital contributions from the nitrogen lone pair.

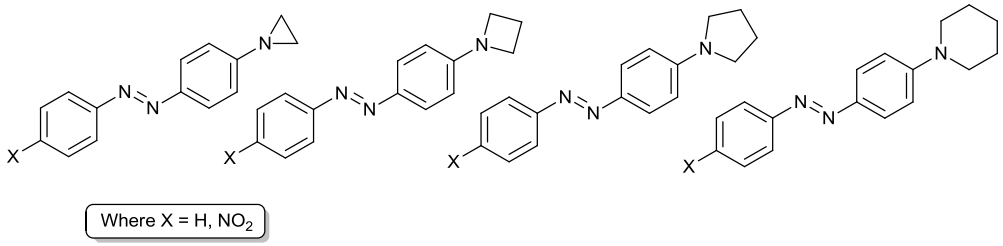
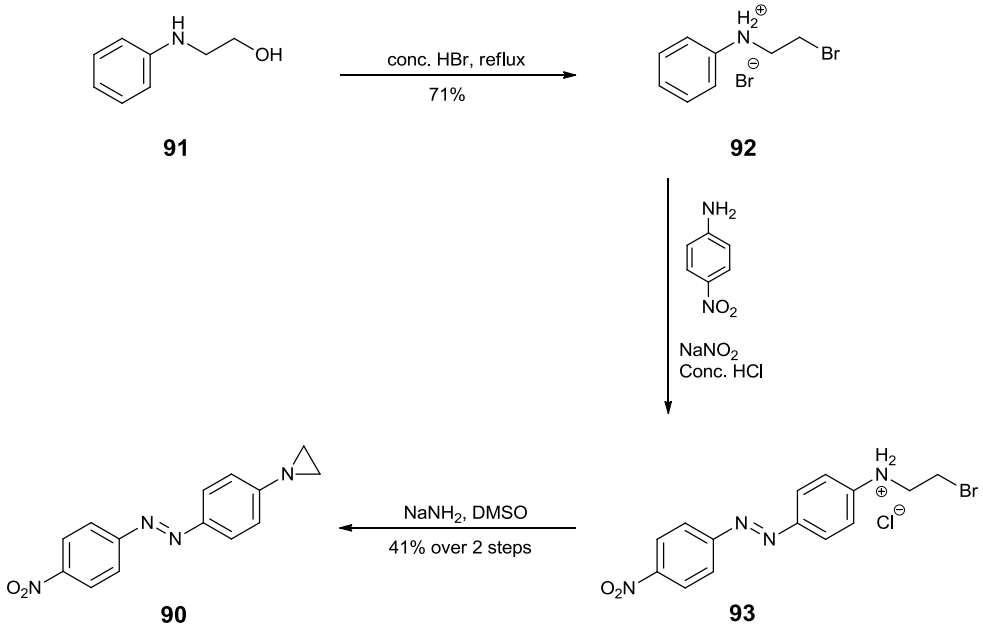


Figure 1.14. Cyclic terminal groups in azobenzenes.[99]

Hallas made various derivatives from three to six membered rings (Figure 1.14), however, only those based on aziridines exhibited unusual properties whereby the ring strain was sufficient to force the nitrogen to be pyramidal. The unique hypsochromic properties of the aziridyl azobenzenes are dependent on solvent and lend credence to the idea that nitrogen delocalization into the azobenzene system is occurring.

Both of our target systems have an aziridine ring connected directly to a fairly simple azobenzene. To maximize the effect of conjugation with the second aromatic ring, we chose to introduce a nitro group in the *para* position of the second ring.

The synthesis of **90** has previously been reported[94] by Hallas during his investigations. Hydrobromide salt **92** was synthesised using a procedure developed by Pearlman, although the reported details were sketchy (Scheme 1.34).[100] Heating of *β*-hydroxy ethylaniline (**91**) in concentrated aqueous hydrogen bromide resulted in displacement of the hydroxyl group and formation of hydrobromide salt **92**. Azo coupling of **92** with *p*-nitroaniline was reported with only small amounts of the hydrolysis side product being observed. Finally, the aziridine ring was closed by treatment of **93** with sodium amide in DMSO.

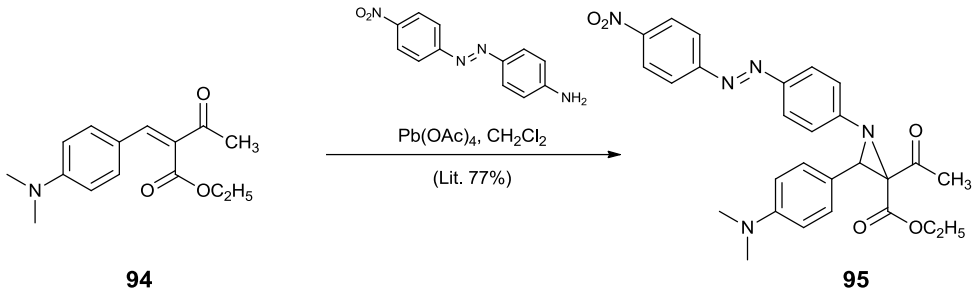


91 **92** **90** **93**

Scheme 1.34. Reported synthesis of **90**.[94]

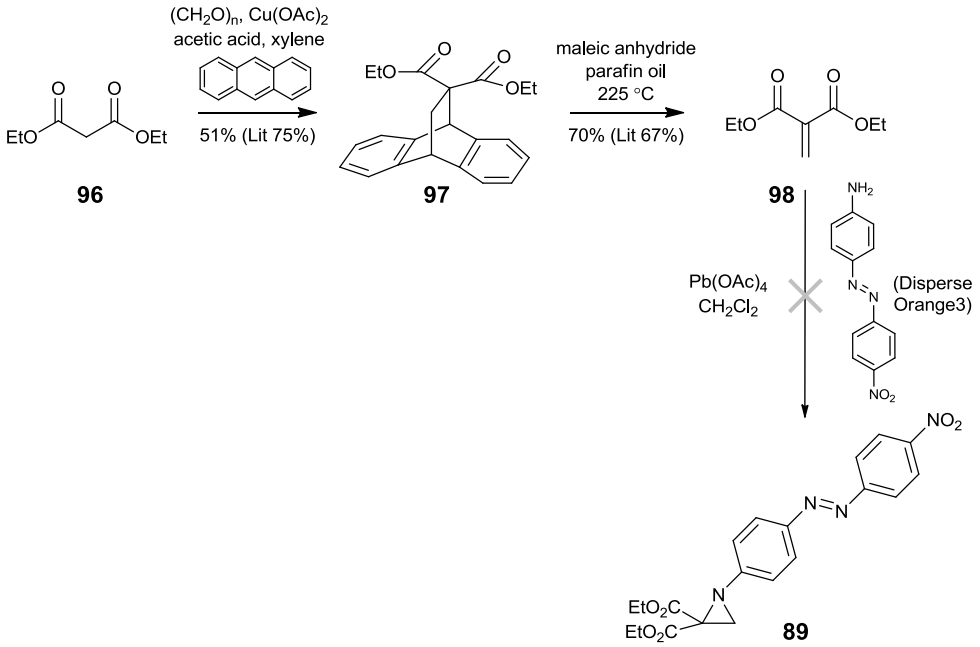
*1.2.5.2 Towards the Synthesis of Aziridine **89***

α,β-Unsaturated esters have been aziridinated using the required amino azobenzene system with lead tetraacetate (Scheme 1.35).[101] The role of the dimethylaminobenzene group on the olefin in this reaction was uncertain. For our requirements, this substituent needed to be removed.



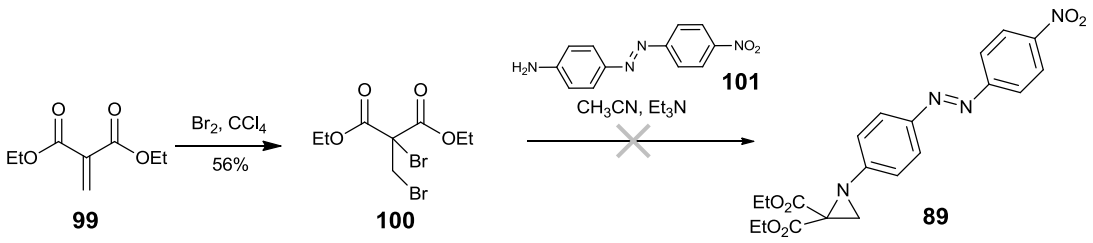
Scheme 1.35. Literature example of $Pb(OAc)_4$ aziridinations.[101]

Diethylmalonate was condensed with paraformaldehyde then immediately trapped by [4+2] cycloaddition with anthracene. The isolated adduct was then heated to 225 ^{o}C to encourage a thermal retrocyclisation and the olefin isolated by distillation according to published methods.[102] A solution of olefin and Disperse Orange 3 (Aldrich) in dichloromethane was treated with lead tetraacetate, however, disappointingly no aziridine products were observed (Scheme 1.36).



Scheme 1.36. Synthetic route towards **89**.[102]

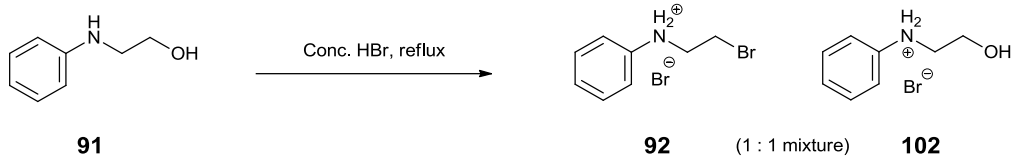
There have been reports[103] of forming aryl aziridines from similar compounds *via* the dibromide. Olefin **99** was brominated in 56% yield using bromine in carbon tetrachloride (Scheme 1.37). Further reactions of **100** with Disperse Orange 3 **101** in acetonitrile clearly showed substitution of one bromine by mass spectrometry (m/z = 493 [^{79}BrM+H]$^+$, 495 [^{81}BrM+H]$^+$, however no conditions were found that promoted the second displacement to form the aziridine ring. At this juncture, we decided to focus on the synthesis of known aziridine **90**.



Scheme 1.37. Attempted alternate synthesis of **101**.

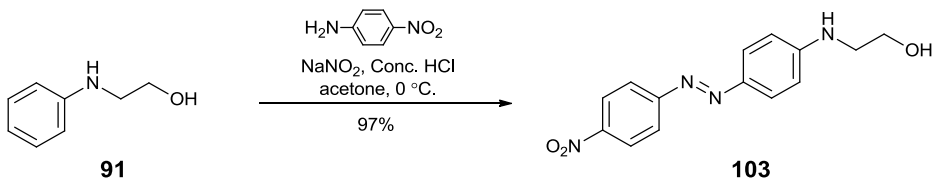
*1.2.5.3 Synthesis of Aziridine **90***

The synthesis of **90** has previously been reported by Hallas[94] (Scheme 1.34). However the synthesis of **90** used a procedure first reported by Pearlman.[100] Unfortunately, in our hands it was not possible to isolate **92** and the best outcome was a 1:1 mixture of **92** and alcohol **102**. Attempts to purify this mixture by fractional crystallisation were unsuccessful (Scheme 1.38**)**.



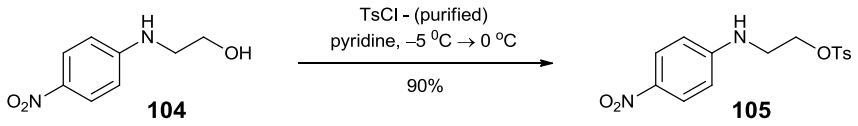
Scheme 1.38. Attempted synthesis of **92**.

Next, we attempted to modify the published route by attempting the diazo coupling using aniline **91**. First, *p*-nitro aniline was treated with sodium nitrite to form the diazonium salt, which was then slowly added to *β*-hydroxyethylaniline (**91**). A deep red solid, **103**, was collected in 87% yield. In an attempt to intercept the developed synthesis, azobenzene **103** was treated with phosphorous tribromide. Unfortunately, this was unsuccessful, most likely due to the high water solubility of the product salt. Basification of the mixture with sodium hydroxide after work-up led to the isolation of **103**, presumably as a result of displacement of the bromide by hydroxide.



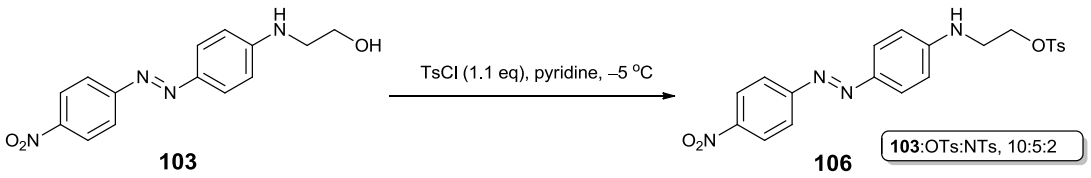
Scheme 1.39. Diazo coupling of **91**.

In order to introduce an alternate electrophile for ring closure, we attempted the tosylation of **103** using 1 eq of purified tosyl chloride at room temperature. However, the result was not encouraging as the major product was the unwanted *N*-tosylated isomer, although trace amounts of the *O*-tosylate were detected. Assigning the products was challenging due to the IR spectral similarities. The *O*-tosylated product is characterised by a widening separation of the CH_2 signals and a downfield shift of these methylenes (3.35 and 3.85 ppm) to 3.50 and 4.20 ppm. The NH signal also moves upfield from 4.70 ppm to 4.50 ppm. The *N*-tosylated product is characterised by the CH_2 signals moving closer together, forming a multiplet centred around 3.65 ppm. Selective tosylation of the oxygen of amino alcohols such as **104** is possible when the aryl substituent is strongly electron withdrawing (Scheme 1.40).[104]



Scheme 1.40. Literature method for selective tosylation.[104]

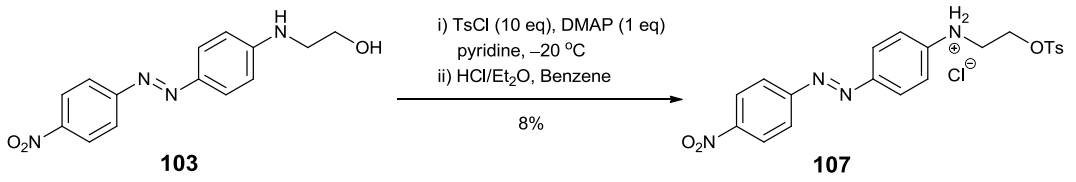
These conditions were then examined using aminoalcohol **103**. Using 1.1 eq of purified tosyl chloride and the reaction cooled to –5 °C (ice / salt water), resulted in a mixture of compounds but predominantly *O*-tosylation was observed with a large proportion of starting material remaining (**103**:OTs:NTs, 10:5:2) (Scheme 1.41).



Scheme 1.41. Selective tosylation of **103**.

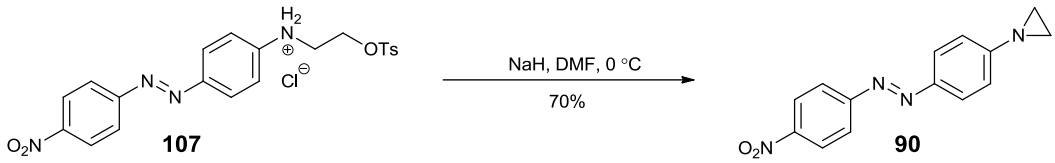
To try and improve the selectivity, mesyl chloride was tried at −78 °C, however, only the unwanted sulphonamide was observed. Treatment of **103** with 1.25 equivalent of tosyl chloride and 10 mol% DMAP in pyridine between −15 and −20 °C showed low conversion but increased selectivity for **106** (**103**:OTs:NTs, 10:5:1). Stirring the mixture for longer did not result in further conversion and warming the mixture to r.t. overnight led to a loss of selectivity. The reaction was repeated but, after 4 hours, a second addition of tosyl chloride (1 eq) and catalytic DMAP was added and the mixture stirred at −20 °C for a further 4 hours to give a 70% conversion, as indicated by crude ^{1}H NMR. Whilst the additional equivalents of tosyl chloride helped force the reaction towards completion, it also brought about the appearance of a di-tosylated product, characterised by CH_2 signals at 4.10 and 3.80 ppm.

To make the reaction method more convenient the procedure was further modified and a solution of **103** was cooled to −20 °C before 10 equivalents of tosyl chloride and 1 equivalent of DMAP were added. The mixture was strictly temperature controlled such that it never warmed above −15 °C and stirred for 6 h. The mixture was quenched at −20 °C by the addition of methanol to trap the excess tosyl chloride. Chromatography, followed by crystallisation of the corresponding HCl salt, provided **107** in 8% yield. The yield was unfortunately significantly impacted due to the difficulty in removing **103** from the product mixture, as the crude ratio was much better (**103**:OTs:NTs:di-tosylate, 1:6:2:2).



Scheme 1.42. Modified synthesis of **107** salt.

Hallas *et al*[96] had reported the effective ring closure of bromide **93** using sodium amide in dimethyl sulfoxide, however this was found to be ineffective in this instance. Other reports indicated the use of sodium hydride in DMSO as also being effective.[104] Whilst the reaction in DMSO did produce some aziridine, the conversion was limited to 44%. Treatment of **107** with sodium hydride in dimethyl formamide, on the other hand, proceeded rapidly with a high conversion (84%). Some ring opening of the aziridine occurred during purification, causing contamination and a reduced yield, but treatment of the chromatography silica with triethylamine and base washing all glassware prevented such ring opening reactions, yielding aziridine **90** in 70% yield. At this junction, the stage was set to explore the impact of light on rates of pyramidal motion.



Scheme 1.43. Ring closure of **107**with sodium hydride.

1.2.5.4 Computational Modeling

Through collaboration with Dr Walsh, an Associate Professor of BioNanotechnology at Deakin University, Australia, it has been possible to calculate the lowest energy ground state structures and transition state structures for both the *cis* and *trans*

azobenzene isomers in a solventless environment and also using an implicit solvent model (toluene). A high level of theory, MP2/6-31G*, was used to optimize the geometry of the minima and corresponding transition state. Single-point energies (SPE) for these optimized structures were then calculated at the higher MP2/aug-cc-pVDZ level. The ground and transition state structures of the *trans* isomer were relatively straightforward to calculate due to the restricted degrees of freedom (Figure 1.15). Conversely, because of the anticipated twist between the aromatic systems in the *cis* isomer, the minimum structure proved more difficult to locate.

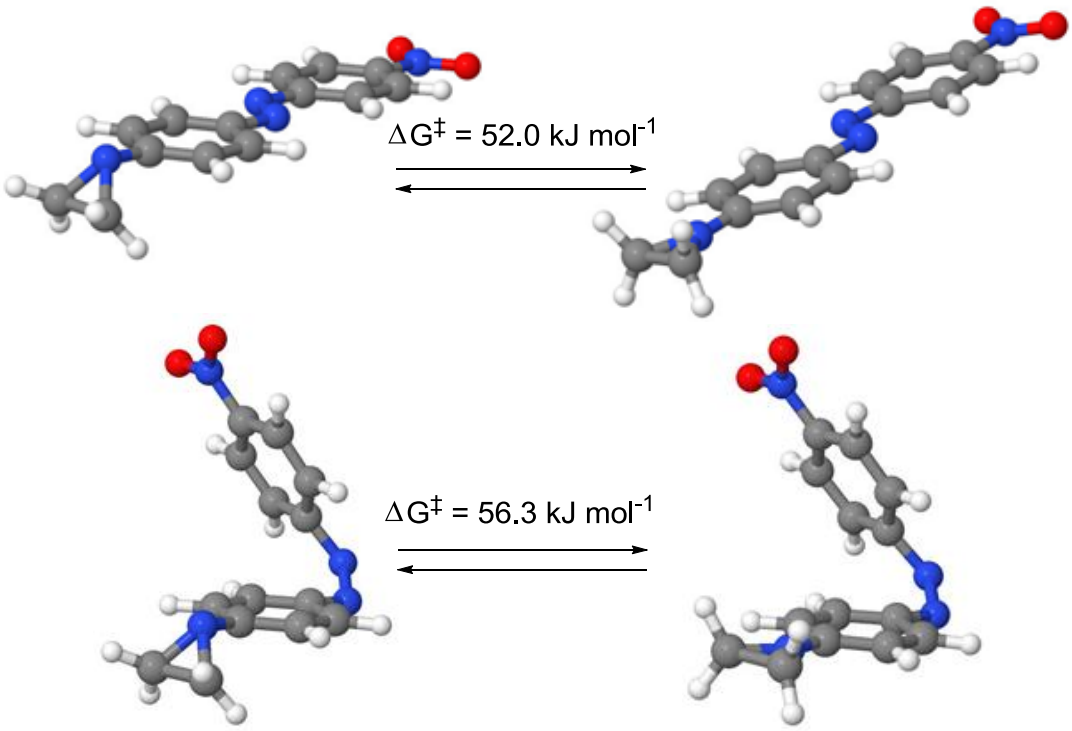


Figure 1.15. Computed ground (Left) and transition (Right) state structures for the *trans* (Top) and *cis* (Bottom) isomers in the gas phase.

The relative energies of these structures were calculated both without solvent and using toluene as an implicit solvent, in order to better model the experimental VT-NMR conditions. The calculated values are shown in Table 1.1 which also shows the

difference in the calculated inversion barriers between the *cis* and *trans* isomers to be 3.6 kJ mol^{-1} at the highest level of theory.

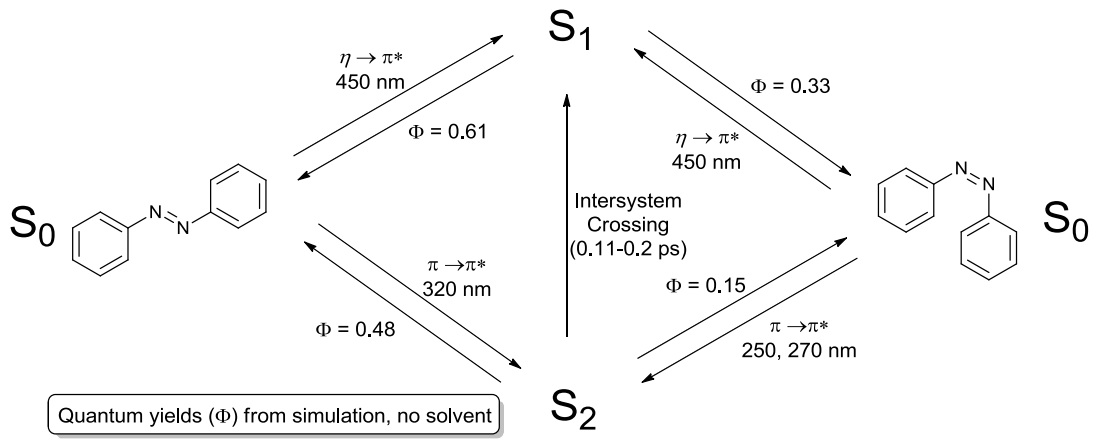
	No Solvent				Implicit Solvent (toluene)			
	E-GS (au)	E-TS (au)	ΔE (au)	$\Delta G^{\ddagger}$ (kJ mol^{-1})	E-GS (au)	E-TS (au)	ΔE (au)	$\Delta G^{\ddagger}$ (kJ mol^{-1})
Trans	-907.545	-907.526	0.0198	52.0	-907.355	-907.337	0.0188	49.3
Cis	-907.530	-907.509	0.0206	56.3	-907.339	-907.319	0.0201	52.9
$\Delta\Delta G^{\ddagger}$				4.3				3.6

Table 1.1. Calculated activation energies for *cis*- and *trans*-**90**.

Importantly, the computed structures of *cis*-**90** and *trans*-**90** validate our initial hypothesis that the *trans* isomer would be planar and highly conjugated, and that the *cis* isomer requires the rings to twist slightly out of plane to each other. Such a twisting clearly disrupts the character of the π system, which is evidenced in the calculated difference in the inversion barriers for the two isomers.

*1.2.5.5 Photochemical Isomerization of **90***

Photoisomerisation of *trans* azobenzenes can proceed *via* two distinct pathways, either a higher energy, sharper $\pi \rightarrow \pi^*$ symmetry allowed transition, or a lower energy, symmetry disallowed and broader $n \rightarrow \pi^*$ transition. For azobenzene, these transitions are well resolved from each other. *Cis* azobenzene has two weaker $\pi \rightarrow \pi^*$ bands at a higher energy than the *trans* isomer, but a strong $n \rightarrow \pi^*$ transition in approximately the same region as the *trans* isomer.



Scheme 1.44. Azobenzene photoisomerisation[88,105] with quantum yields.[106]

The UV/VIS spectrum of aziridine *trans*-**90** was poorly resolved, indicating overlap of electronic transitions. Many substituted azobenzenes have very similar UV/VIS spectra to azobenzene.[88] The $\pi \rightarrow \pi^*$ *trans* → *cis* is at a longer wavelength, separated from $\pi \rightarrow \pi^*$ *cis* → *trans.* Also, the $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transitions for both isomers are well separated, allowing for the selective excitation of either the *cis* or *trans* isomer. Typically, the broad $n \rightarrow \pi^*$ transitions above 400 nm overlap, but normally favour formation of the *trans* isomer due to the significantly higher quantum yields and a stronger absorbance. Narrow ranges of wavelengths can be used to selectively target the $\pi \rightarrow \pi^*$ transition of either isomer, allowing control over the direction of the

isomerisation and achieving high photostationary ratios. Unfortunately, it has been reported that in 2- and 4-amino azobenzenes, the $\pi \rightarrow \pi^*$ transition shifts to longer wavelengths and overlaps with the $n \rightarrow \pi^*$ transition.[107] This is clearly the case for compound *trans*-**90**, as the spectra shown in Figure 1.16 is very broad and poorly resolved.

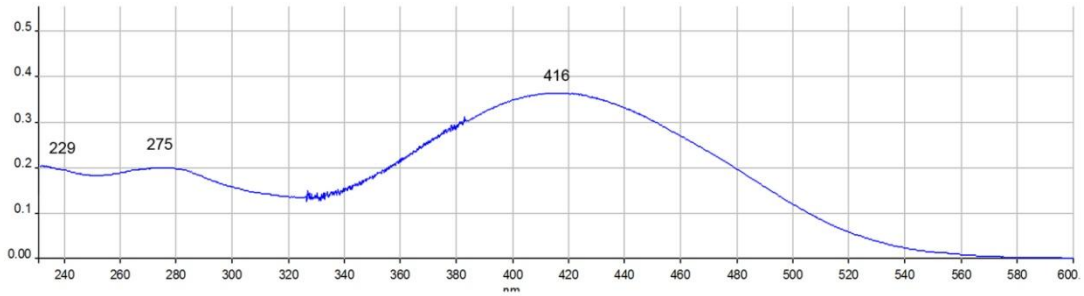
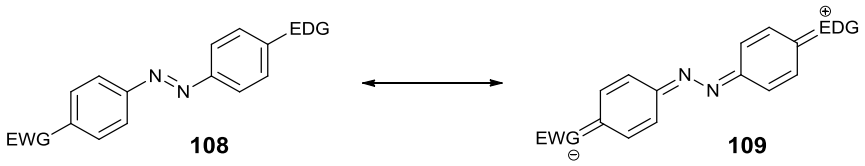


Figure 1.16. UV trace of compound **90**.

Aziridine *trans*-**90** was dissolved in deuterated dichloromethane in an NMR tube and irradiated using a 125 W medium pressure Hg lamp, initially using a <355 nm cutoff filter (0.0012 M $BiCl_3$ in 4.8 M HCl) and then separately with a >360 nm cut off filter (0.8 M $NiSO_4$ + 1.0 M $CoSO_4$).[108] Both reactions were irradiated at room temperature for 1 h. Following irradiation the sample was kept in the dark and immediately studied by ^{1}H NMR spectroscopy (within 5 min), however, no *cis* isomer was detected.

A subclass of azobenzenes are the push-pull azobenzenes and are characterized by an electron withdrawing group on one of the aromatic rings and an electron donating group on the other. These molecules have been shown to have very thermally unstable *cis* isomers compared to other azobenzenes. One explanation is that delocalisation of the electron density by resonance for isomer *cis*-**90**, leads to a higher degree of N-N single bond character. The extreme case is shown in Scheme

1.45. This allows for rotation to occur, leading to the thermodynamically more stable *trans* isomer. Whilst the partial isolation of the π systems in the *cis* isomer would limit this delocalisation, some degree of N-N π-bond disruptive character probably exists.[88]



Scheme 1.45. Delocalisation of electron density in azobenzenes.

In such push-pull systems, use of solvents with a small dielectric constant are found to significantly increase the lifetime, up to a 10,000 fold, of the *cis* isomer. Presumably this is due to a reduction in stabilization of the polarised resonance form **109** through solvent interactions.[93,109]

Toluene-d_8 is an ideal solvent, with a useable NMR range down to –95 ^{o}C and, at the same time, is known to be amongst the best at extending the lifetime of diazo *cis* isomers.

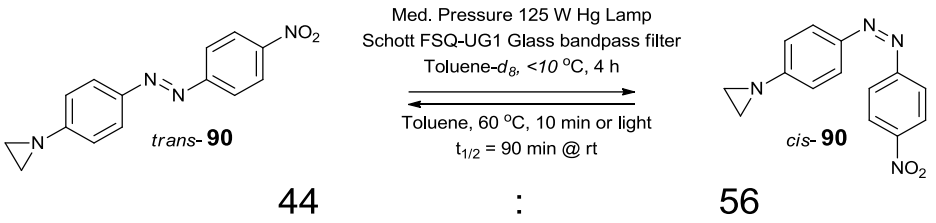
When *trans*-**90** was dissolved in benzene-d_6 and irradiated (room temperature, 1h) using the >360 nm cut off filter (0.8 M $NiSO_4$ + 1.0 M $CoSO_4$), a small amount of *cis*-**90** was observed (*trans* : *cis*; 90 : 10). When the experiment was repeated using the < 355 nm filter (0.0012 M $BiCl_3$ in 4.8 M HCl), this conversion increased (*trans* : *cis*; 81 : 19). A more complicated bandpass filter has been reported using 0.75% w/v iodine in carbon tetrachloride,[110] which has a modest transmission of ~ 40%, but is highly selective for λ_{max} = 390 nm ($\lambda_{1/2\ max}$ = 350, 410 nm). Irradiation of *trans*-**90** in

toluene (room temperature, 1 h or 2 h) through this filter resulted in further improvement of the conversion (*trans* : *cis*; 73 : 27). The thermally induced back reaction could be inhibited by use of lower photoirradiation temperatures. Indeed, photoirradiation of *trans*-**90** and keeping the surrounding filter solution at <10 °C (ice-water bath) for 3 h, improved the isomerisation such that *cis*-**90** was the major product (*trans* : *cis*; 44 : 56), (48 : 52, toluene-d_8). No further improvements were seen lowering the temperature to –20 °C.

Next, we explored the effect of increasing the intensity of the light source. The Schott FSQ-UG1 UV bandpass filter has transmission properties almost identical to the iodine/carbon tetrachloride solution filter, but with a much higher maximum transmission of 75%.[111] Using a box around the lamp, and this glass as a window, the sample was irradiated under the same conditions in toluene with cooling in ice/water. However, no improvement in the conversion was observed.

At room temperature, *cis*-**90** isomerised to *trans*-**90,** according to the expected first order kinetics, $t_{1/2}$ = 90 min ± 10 min in toluene with k = 0.0002 s^{-1} (see Appendix 3). This is significantly slower than values reported for classical push-pull azobenzenes,[93] demonstrating the effect of ring strain on the ability of the nitrogen to delocalise into the π-system. Below 10 ^{o}C, the *cis* isomer was observed to be thermally stable, which importantly simplified low temperature VT-NMR experiments as the *cis*-**90** isomer did not revert to *trans*-**90** during the long experiment time.

The photoisomerisation of **90** was optimised, however only a maximum ratio of *trans* : *cis*; 44 : 56 was achieved using a λ_{max} = 390 nm filter, 125 W Hg lamp, temperature <10 °C, irradiated for 4 h. This is imperfect, but is most likely close to the achievable limit for this compound with the thermal instability of *cis*-**90**, and overlapping excitation wavelengths of the isomers, making further improvement difficult. The *cis* → *trans* isomerisation was easily achieved thermally by placing the sample in a 60 °C oil bath for 10 min.



Scheme 1.46. The optimised isomerisation of **90**.

1.2.5.6 Determination of Activation Parameters for Pyramidal Inversion

The four hydrogens of an unsubstituted aziridine are all magnetically non-equivalent, resulting in a highly second order AA'BB' spin system. WinDNMR and the equations method are not suitable for simulating such complex spin systems.[77] These spin systems have been observed for a number of aziridines, including simple NH aziridine.[39,112,113] Fortuitously, when low temperature ^{1}H NMR spectra for *trans*-**90** were acquired, the aziridine signals were observed as two singlets of a simple A_2B_2 spin system, coalescing to one singlet at higher temperatures. Presumably $J_{AB} = J_{AB'}$ making A and A' both chemically and magnetically equivalent.

The activation parameters of *trans*-**90** and *cis*-**90** were calculated using the aziridine ^{1}H signals in two ways. Firstly, using the simple coalescence method, and later using

the more accurate line shape analysis. Equation 1.2 only requires accurate determination of the coalescence temperature (T_c) and the maximum separation of the fully resolved signals. At the lowest possible VT-NMR temperature, the signals for both isomers were still somewhat broad, however this was more pronounced for *trans*-**90**. For *cis*-**90**, determination of T_c was more difficult due to the presence of both isomers in the sample and overlapping of some signals. Attempts were made to electronically subtract the spectra of *trans*-**90** from the spectra of the mixture but without success. These issues somewhat increase the uncertainty of values calculated using this method.

$$\Delta G^{\ddagger} = RT_c[23 + \ln(\frac{T_c}{\Delta \nu})]$$

Equation 1.2. Where R is the gas constant and $\Delta\nu$ is the maximum separation of resolved signals.

A major limitation of the equation method is the inability to calculate $\Delta G^{\ddagger}$ at temperatures other than T_c. Commonly, systems to be compared have different T_c values which makes comparison difficult. In the case of pyramidal inversion, the entropy term is normally small, making variations over temperature ranges smaller, and more manageable.

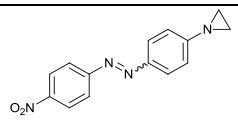
	T_c (K)	$\Delta G^{\ddagger}$ at T_c (kJ mol^{-1})
Trans-***90***	207	38.9
Cis-***90***	223	42.2

Table 1.2. Calculated activation parameters at coalescence using the T_c equation method.

Using this method, $\Delta\Delta G^{\ddagger} \approx 3.3$ kJ mol^{-1} was determined with the *cis* isomer having a higher barrier to inversion. Data was consistent with that predicted, and in line with

values computed previously. Complete line shape analysis is commonly regarded as a superior method to derive activation parameters. Line shape fitting calculates the rate of a process from Heisenberg uncertainty broadening. This is done over a wide range of temperatures, thus allowing $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ to be determined from a plot of the Eyring equation. Spectra were acquired from 219 to 188 K, and the measured spectra fitted to line shape analysis using the A_2B_2 spin system with WinDNMR.[77]

(1.8) $$k = \frac{k_B T}{h} e^{-\frac{\Delta G^{\ddagger}}{\mathrm{RT}}}$$

(1.9) $$\ln \frac{k}{T} = \frac{-\Delta H^{\ddagger}}{\mathrm{R}} \cdot \frac{1}{T} + \ln \frac{k_B}{h} + \frac{\Delta S^{\ddagger}}{R}$$

Figure 1.17. The Eyring equation (1.8) and its linear form (1.9).

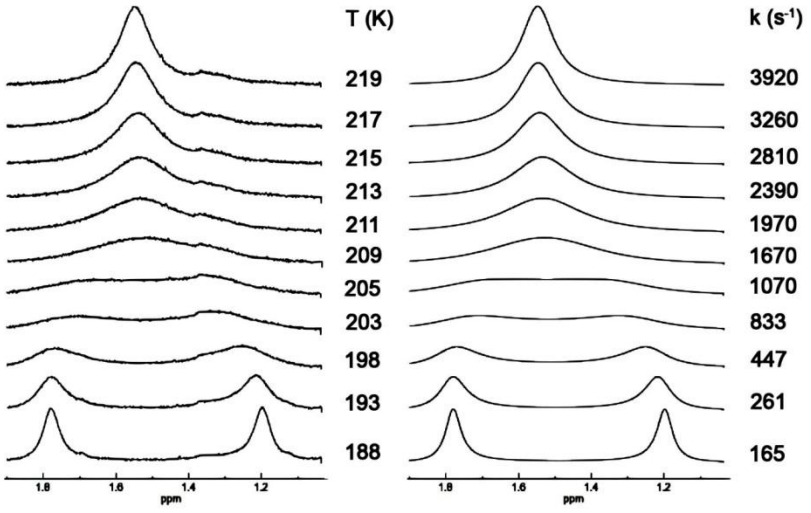


Figure 1.18. Correlation of actual (left) and simulated (right) spectra were excellent for the *trans* isomer allowing the rate of inversion to be calculated for a range of temperatures.

Processing the VT-NMR data for *cis*-**90** was more difficult. Once the photochemical reaction was complete, the sample was wrapped in foil and stored in dry ice/acetone then transported to the NMR spectrometer, which was precooled to 188 K.

Unfortunately, *cis*-**90** contained *trans*-**90** (56 : 44), complicating the analysis. Upon warming the sample, it was clear that *cis*-**90** coalesced at a higher temperature, however, close to $T_{c,}$ the broad signals overlapped, therefore making simulation difficult. These temperatures were omitted from the Eyring plot in order to reduce the uncertainty. However, as can be seen, the data above and below this region are very good, allowing $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ to be determined.

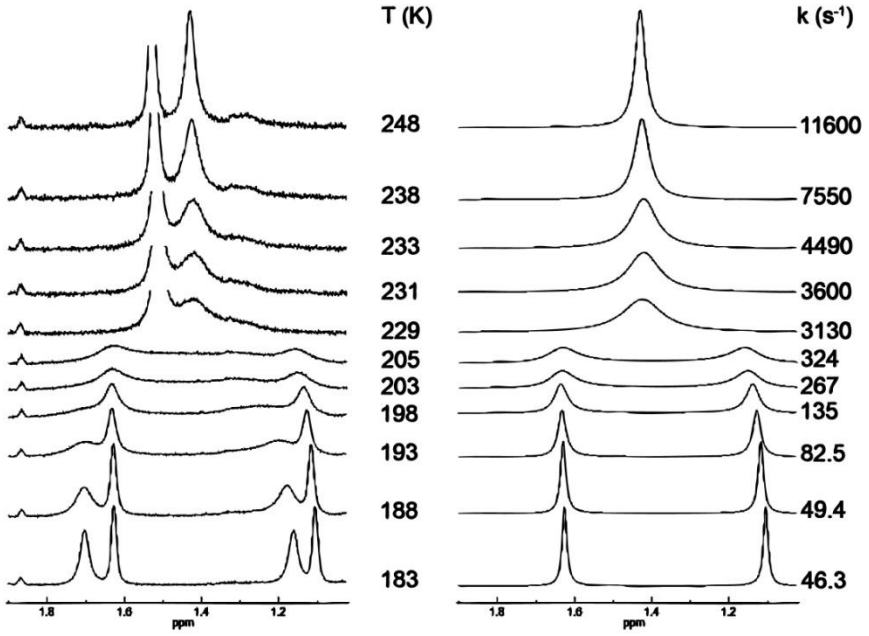
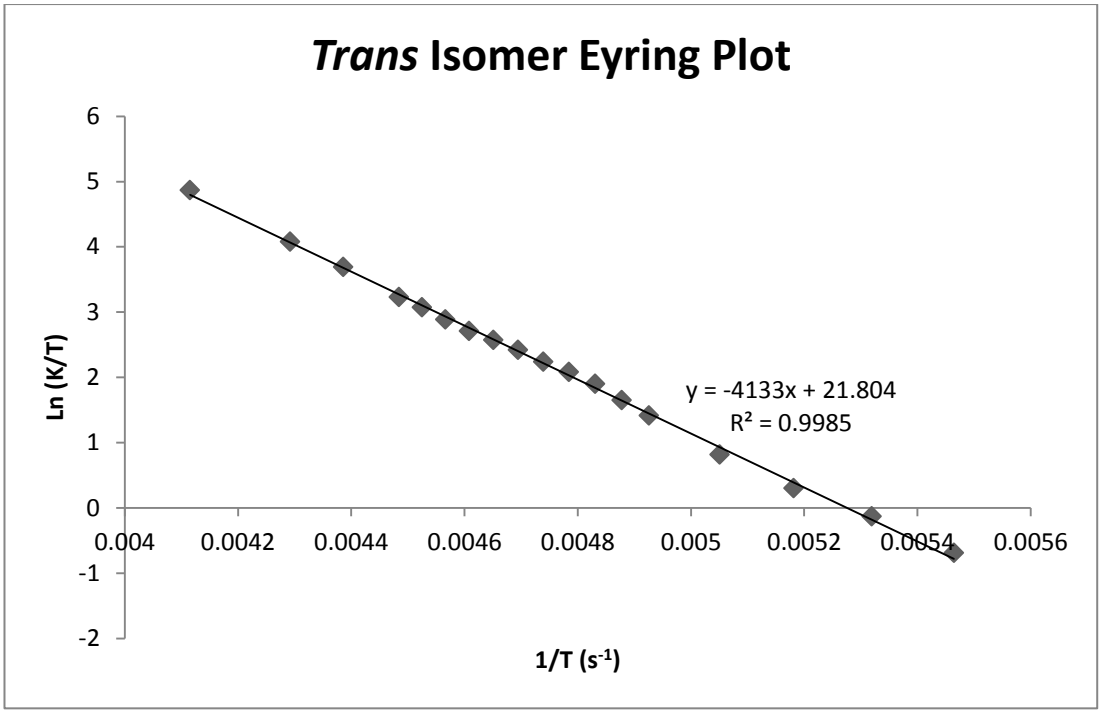
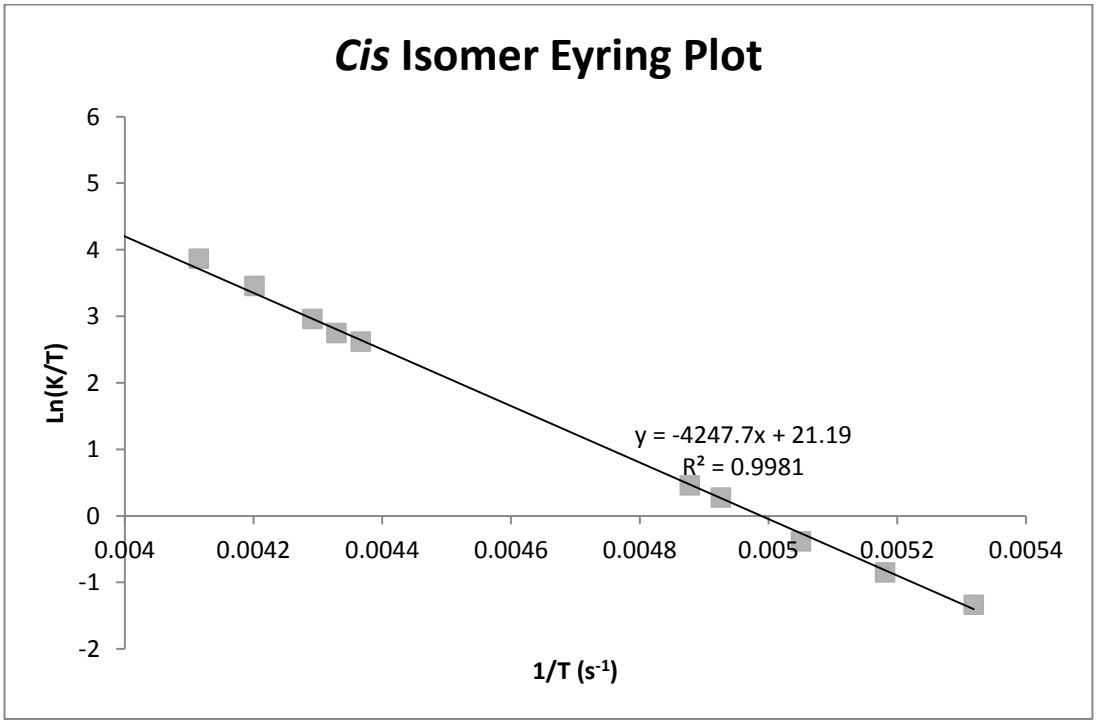


Figure 1.19. Correlation of actual (left) and simulated (right) spectra for the *cis* isomer, allowing the rate of inversion to be calculated for a range of temperatures.

Because the Eyring plots 1.1 and 1.2 give $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ as functions of the gradient and intercept it is possible to calculate $\Delta G^{\ddagger}$ at any temperature. Table 1.3 shows that the line shape data has been calculated for each coalescence temperature, allowing for comparison with the data compiled from the equations method. This shows that whilst the absolute values for $\Delta G^{\ddagger}$ are smaller when extracted from line shape fitting, the relative difference between the two isomers is similar, but about 1 kJ mol^{-1} less than when comparing coalescence temperature calculations.



Graph 1.1. Eyring plot generated from rate data obtained by line shape fitting of *trans*-**90**.



Graph 1.2. Eyring plot generated from rate data obtained by line shape fitting of *cis*-**90**.

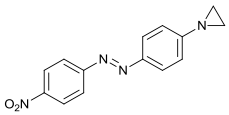
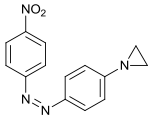
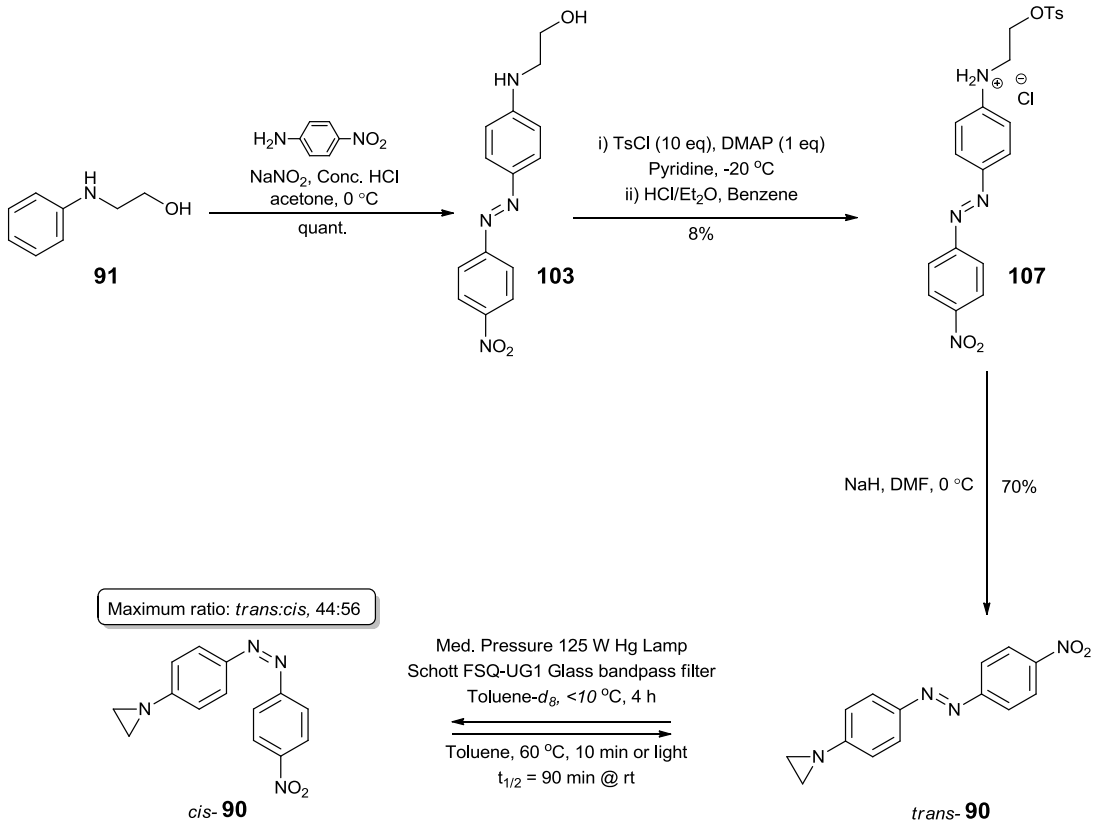
	$\Delta G^{\ddagger}$ (207K) (kJ mol^{-1})	$\Delta G^{\ddagger}$ (223K) (kJ mol^{-1})	$\Delta G^{\ddagger}$ (298K) (kJ mol^{-1})	$\Delta H^{\ddagger}$ (kJ mol^{-1})	$\Delta S^{\ddagger}$ (J K^{-1} mol^{-1})
 (T_c = 207)	37.7	38.0	39.2	34.4	-16.3
 (T_c = 223)	39.7	40.1	41.7	35.3	-21.4

Table 1.3. Calculated activation parameters based on line shape fitting data.

At 298 K, there is a 2.5 kJ mol^{-1} difference in the inversion barrier between *trans*-**90** and *cis*-**90**. Using the Eyring equation, this equates to a ~ 2.8 fold difference in the inversion rate (k = 8.3 x 10^5 vs 3 x 10^5 s^{-1}). This represents a significant change in the rate of pyramidal inversion, which results from the photochemically induced isomerisation. Aziridine **90** is very robust when kept away from sources of acid. It can be rapidly cycled to *cis*-**90** with light and back to *trans*-**90** by heating it in an oil bath at 60 ^{o}C for 10 minutes. Three complete cycles were completed without any sign of degradation.

1.2.5.7 Conclusions

Azobenzene containing aziridine **90** has been successfully synthesized *via* a modified synthetic pathway in 3 steps from **91**. The photoisomerisation of **90** has been optimised to the following conditions. Irradiation for 4 h with a 125 W Hg lamp through a λ_{max} = 390 nm filter with the solution cooled to <10 ^{o}C (ice/water). The thermal isomerisation of *cis*- **90** has also been optimised to 10 min at 60 ^{o}C.

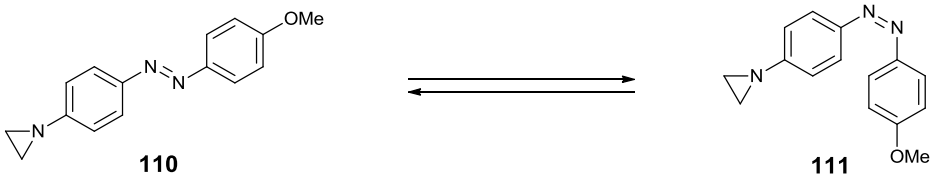


Scheme 1.47. Synthetic route to **90** and photochemistry.

It has been demonstrated that it is possible to modify the pyramidal inversion rate of this molecule using only the physical inputs of light and heat. This process proceeds without degradation and can be cycled at least three times sequentially. This represents the first example of photocontrolled pyramidal inversion. The standard Gibbs free energy of activation for *trans*-**90** (39.2 kJ mol^{-1}) and *cis*-**90** (41.7 kJ mol^{-1}) has been determined using complete line shape fitting. A difference in the Gibbs

free energy of activation between the two isomers equal to 2.5 kJ mol^{-1} has been determined with the *cis* isomer having a higher activation barrier. This equates to >2.8 fold difference in the rate at 298 K. The experimental values are supported by computational methods, which slightly overestimated the difference in the activation barrier ($\Delta\Delta G^{\ddagger}$ = 3.6 kJ mol^{-1})

However, there is still significant scope for development since the *cis* isomer is less thermally stable ($t_{1/2}$ = 90 min at 298 K) than hoped, due to the push – pull nature of this azobenzene. Only a relatively low conversion to the *cis* isomer can be achieved (ca 56%). Whilst the *cis* isomer appears to be stable below 10 ^{o}C, at room temperature it is found to rapidly revert to the *trans* isomer. It may be possible to solve these problems by moving to a push – push azobenzene system (Scheme 1.48), which could result in a change to the pyramidal inversion for the same reasons. These molecules have been reported to be more thermally stable,[88] however reports,[104] and our own experiments, suggest that an alternative synthetic pathway would be required. This is because it is only possible to complete the selective tosylation step **103** – **107** when there is a directly conjugated and strongly electron withdrawing group in the ring system.



Scheme 1.48. Potential Push-Push azobenzene system.

Chapter 2:

Towards Light-Activated Antimicrobial Agents

2.1 Introduction

2.1.1 Antimicrobial Agents

2.1.1.1 History

β-Lactams are one of the largest families of antibacterial compounds, along with macrolides and fluoroquinolones (Figure 2.1).[114] The serendipitous observations of an apparent bacterial exclusion zone around the fungus *Penicillium rubens* by Fleming in 1928[115] led to the discovery of penicillin. This in turn led to the development of a variety of penicillins and cephalosporins for use as antibiotics.[116]

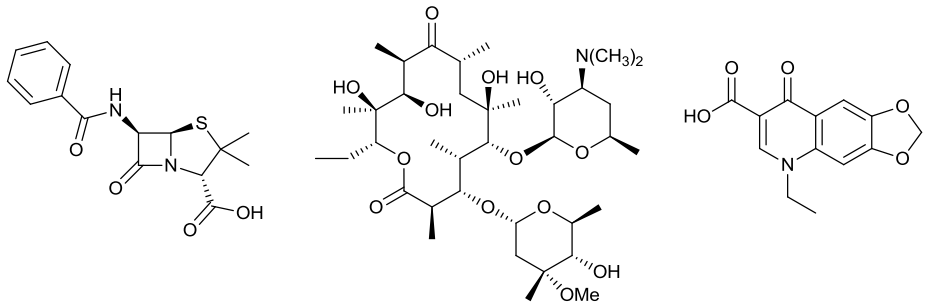


Figure 2.1. Important antibiotic families.

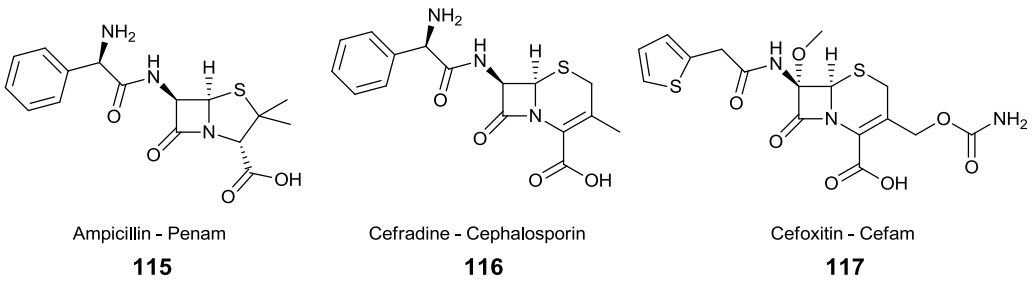


Figure 2.2. Families of commercial *β*-lactam antibiotics.[117]

In order to combat the growing rise of antibiotic resistant bacteria, the cephamycins were developed in the 1970s and were found to be more resistant to *β*-lactamases, which are the origin of bacterial resistance. There followed an explosion in new

classes of *β*-lactams discovered from natural sources, which proved to be both potent and relatively resistant to *β*-lactamases. This prompted further synthetic investigations, which allowed the diversification of existing families and the creation of new ones that were not derived from natural sources, such as the monobactams, carbapenems, cephabacins and formadicins (Figure 2.2).[118]

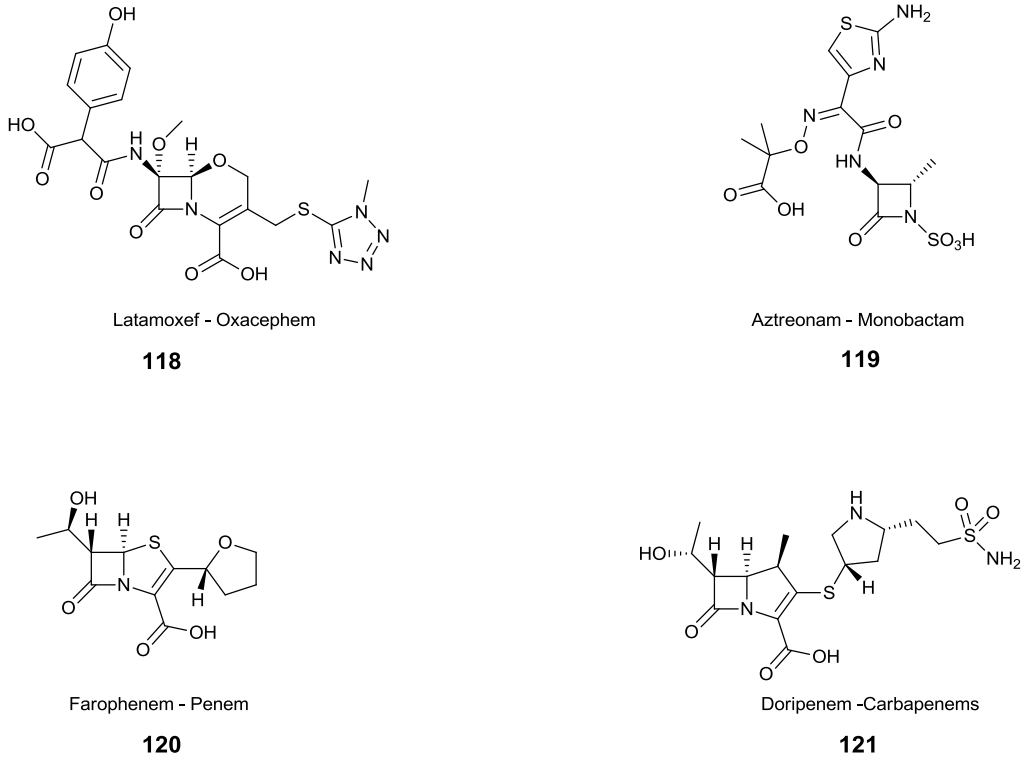


Figure 2.3. Families of commercial *β*-lactam antibiotics.[117]

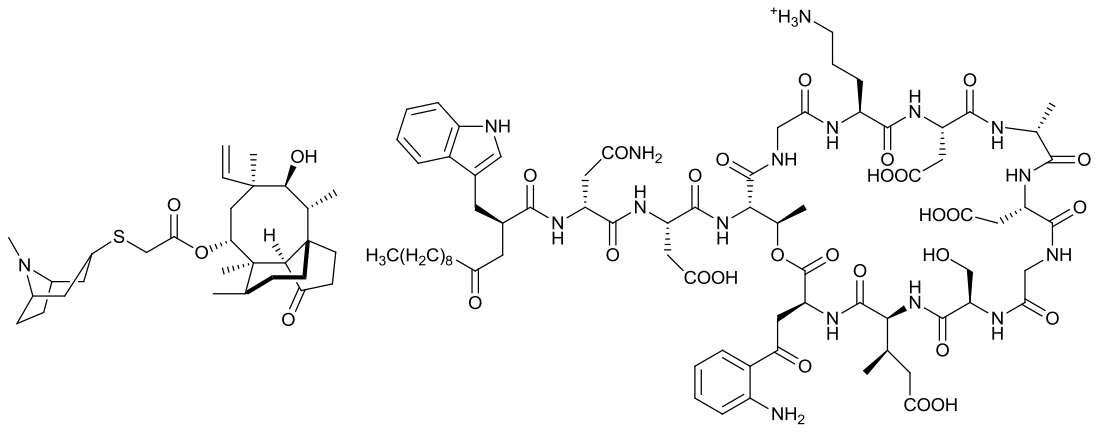
2.1.1.2 Importance in Modern Medicine

At the time of their discovery, penicillin based *β*-lactams were the first drugs capable of treating previously serious bacterial infections from *Syphilis*, *Staphylococci* and *Streptococci*. Since then the diversity of *β*-lactams has greatly increased and subsequently so have the number of infections that can be treated. However,

alongside the increased use of β-lactams, the number of bacteria developing resistance to them has also multiplied.[119]

During the boom years of β-lactam development, huge numbers of antibiotics were developed, along with new methodologies to synthesise them. As the number of new antimicrobial compounds grew, and the number of approved treatments became comprehensive, interest in further development faded.

However, due to the prevalent rise of bacteria resistance to all but a few current products, scientific interest has returned to focus on known and novel families of antibiotics in order to diversify their structures and combat the growing resistance. Recent novel antimicrobial families include the Pleuromutilins **122**[120] and Lipopeptides **123**[121] (Figure 2.4). However, development is very expensive with a low return for the pharmaceutical companies since the new antibiotic families are being reserved as a last line of defence. The introduction of structurally unique β-lactams is another method[122,123] which might help in the fight against antimicrobial resistance, but may also expand the applications of β-lactams into new areas. To go alongside this, new synthetic strategies must be investigated that will allow for facile access to structures quite distinct from common β-lactams.[124-126]



Retapalumin
122

Daptomycin
123

Figure 2.4. Members of the Pleuromutilins (left) and Lipopeptides (right); both new approved treatments against Gram-positive skin infections.

β-lactams are also an important class of compounds beyond their application as antibiotics. The functional *β*-lactam moiety is found in many more biological applications and is a feature of some herbicides[127] as well as showing activity against certain cancer cells.[128] Their high ring strain energy makes them much more reactive than normal amides, making them useful intermediates in the synthesis of more complex products.[129,130] Therefore the development of methodologies towards new classes of *β*-lactams is an important contribution to the knowledge base of organic synthesis.

2.1.1.3 Mechanism of Action

β-lactams work by disrupting the action of transpeptidase enzymes, which cross-link the bacterial cell wall. The rigid cell wall is comprised of alternating *N*-acetylmuramic acid (NAM) and *N*-acetylglucosamine (NAG) units. Each NAM unit has a pentapeptide attached to it, which contains a D-alanine subunit. Two of these D-alanine residues are then cross-linked by the transpeptidase enzyme. These

enzymes, also known as penicillin binding proteins (PBPs), are responsible for the final cross-linking step in the formation of the peptidoglycan layer of the cell wall, which makes it rigid and gives osmotic stability (Figure 2.5).[131]

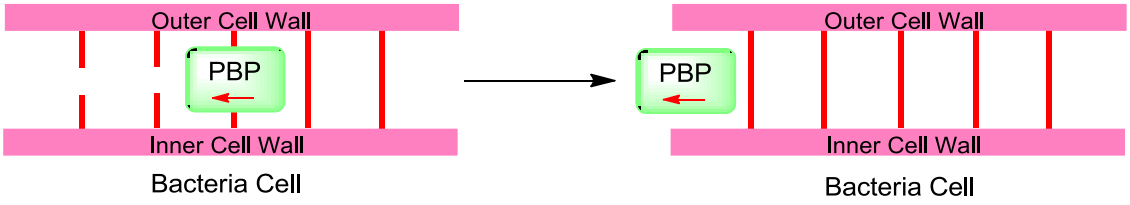


Figure 2.5. Cross-linking of bacterial cell wall.

Without this cross-linking event, the cell wall ruptures, resulting in cell death. The penicillin binding proteins have a high affinity for the *β*-lactams, because the lactam closely mimics the D-alanine – D-alanine region of the NAM pentapeptide. The PBP mistakenly recognises the *β*-lactam molecule as another building block in the cross-linking process, and binds to it. However, once bound, the lactam ring is irreversibly opened causing acylation of the PBP, thereby blocking its function and leaving the bacterial cell wall in a weak state (Figure 2.6).[132]

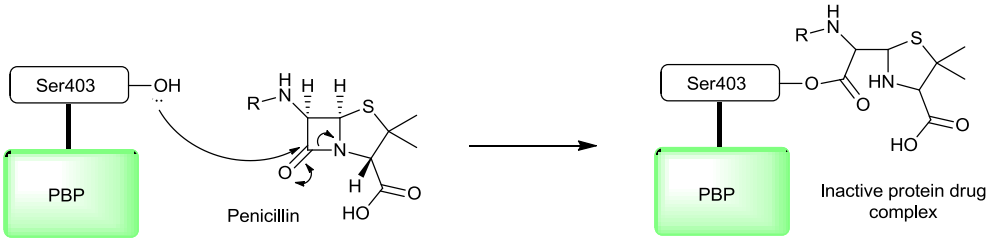


Figure 2.6. Mechanism of action of penicillin.

Infections caused by Gram-positive bacteria are most commonly treated using *β*-lactams because the peptidoglycan layer is the outer, most crucial, layer in the cell wall. Gram-negative bacteria, however, have a second membrane outside of the

peptidoglycan layer, which consists of lipopolysaccharides and proteins. This additional membrane means that Gram-negative bacteria are much less susceptible to *β*-lactam antibiotics because the peptidoglycan layer is less crucial to the stability of the cell wall.[133]

2.1.1.4 Resistance to β-lactams

The growing resistance of many bacteria to *β*-lactam antibiotics is of increasing concern and raises fears of untreatable common infections, similar to those seen before the invention of modern antibiotics. The major causes of resistance to antibiotic medication are largely preventable, however, on a global scale this is proving very difficult to manage. Once drug treatment has been initiated, it is imperative that the treatment is continued until the bacteria are eradicated. If treatment is terminated early, even if symptoms have been alleviated, the surviving bacteria can develop resistance.[134]

It is a stark reminder of the power of evolution that bacteria are able to mutate so effectively over a relatively short amount of time.[135] There are four modes of resistance observed in bacteria.[136] Firstly, it is possible that the penicillin binding protein can be modified so that it is less susceptible to binding with *β*-lactam containing antibiotics, thereby significantly reducing the effectiveness of some drugs. An example of this mode is found in the bacteria *Streptococcus pneumonia*, where natural transformation and recombination of DNA from other organisms has led to PBPs with a low binding affinity for *β*-lactams and therefore a high level of resistance. Horizontal gene transfer has led to a spread of resistance to other related organisms such as MRSA (Methicillin-resistant *Staphylococcus aureus*) bacteria. In

most cases, resistance evolves against specific *β*-lactam families, which still allows successful treatment with structurally different *β*-lactams.[137]

Another mode of resistance is the production by the bacteria of other proteins with the express purpose of destroying the *β*-lactams by hydrolysis. This is one of the most common modes of defence, especially amongst Gram-negative bacteria, which are the hardest to treat. These so-called *β*-lactamases can be very efficient at hydrolysing the *β*-lactam ring before the drug is able to act. This can be overcome by delivering the antibiotic with a *β*-lactamase inhibitor such as clavulanic acid, Sulbactam, Tazobactam and Aztreonam (Figure 2.7).[138] Azetreonam was originally developed as a stand alone antibiotic, however, it was found to be an efficient inhibitor as it is readily ring opened by some *β*-lactamases and has been found to be especially effective at fighting cephalosporinases. These inhibitors are also *β*-lactams, but the interaction with *β*-lactamases must be different in order to be effective. Most *β*-lactamases are able to quickly hydrolyse many molecules of antibiotic without being deactivated, but an effective inhibitor, often called a "suicide inhibitor," must either permanently bind with the *β*-lactamase, or remain in the active site for a prolonged period.

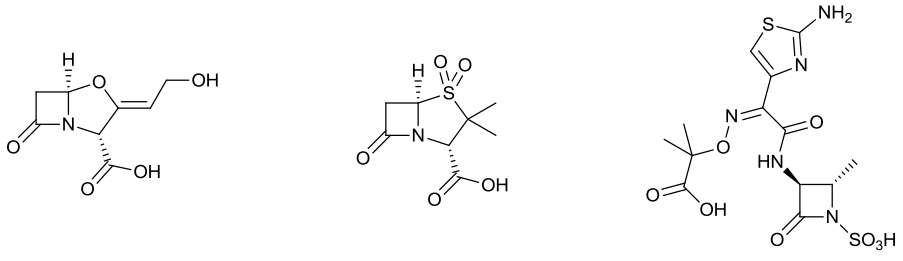


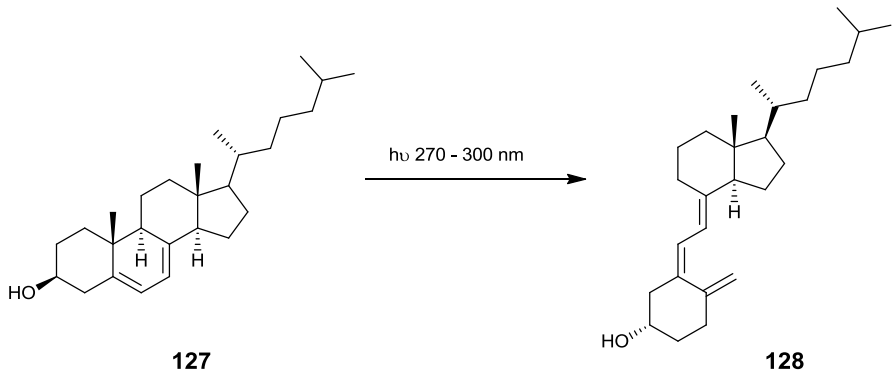
Figure 2.7. Effective *β*-lactamase inhibitors.[139]

For β-lactams to be effective they must diffuse through the outer membrane of the bacterial cell wall in order to access PBPs on the inner plasma membrane. This diffusion is aided by outer membrane proteins on the surface of the bacteria cell. Some bacteria such as *Escherichia coli* have developed resistance to carbapenems by reducing the expression of these outer membrane proteins.[140]

Finally, some bacteria have developed efflux pumps in the cell wall that are capable of removing β-lactams from inside the cell. This can be very effective in Gram-negative bacteria where the additional outer cell membrane already makes it difficult for drug molecules to permeate into the cell.[141]

2.1.2 Photoactivation in Medicine

Radiation has long been used for treatment and diagnosis in medicine. The use of visible or near visible light is a treatment field called phototherapy and is already used to directly treat vitamin D deficiency, neonatal jaundice, autoimmune diseases and bipolar disorder. Indirect phototherapy is an emerging field where an administered molecule absorbs light and the photoexcited molecule undergoes a subsequent range of processes that provide biological activity. This may be a photochemical reaction of the molecule, a photoreaction with surrounding biomolecules or an energy/electron transfer. [142] Vitamin D_3 formation is an excellent example of a biologically active molecule being formed *in vivo* through the action of light[143] (Scheme 2.1).



Scheme 2.1. Photochemical formation of vitamin D_3.

The technology allows for temporal and spacial control of an active compound with the use of a light source. A non-toxic prodrug can be delivered, which ideally bio-accumulates in the target region and can then be activated at the required time using light. Light penetration of human tissue is dependent on a number of factors such as pigmentation, adsorption by haemoglobin and myoglobin, and light scattering. Light of longer wavelength (600-700 nm) penetrates 1.5 - 3 times further than shorter wavelengths (400-500 nm).[144] The prodrug can be activated locally, either topically (in the skin) with broad spectrum lamps, or internally using laser light sources attached to fibre optics.

Cancer treatment is an area of great interest as many anti-cancer agents are also toxic to normal human cells and processes, as well as the targeted cancer cells. If the treatment is confined to the area of the tumour cells, the adverse effects on the rest of the body are more limited.[145] Photodynamic therapy (PDT) is becoming an increasingly important line of anti-cancer research. Where phototherapy uses a prodrug and light, photodynamic therapy relies on a non-toxic sensitizer molecule and a third element, oxygen.[146] Sensitizers are commonly based on porphyrins, [147] a range of which have been approved for clinical use to treat a variety of abnormalities

(Figure 2.8). The sensitizer molecule is excited, commonly with long wavelength (620-850 nm), this energy is then transferred to triplet oxygen, promoting it to cytotoxic singlet oxygen. Singlet oxygen then causes DNA and protein disruption to surrounding cells leading to tumour death. Unfortunately, PDT treatments can be hindered by low oxygen concentrations (common in rapidly growing tumour cells), causing damage to blood components (from singlet oxygen) and poor compound solubility.[148]

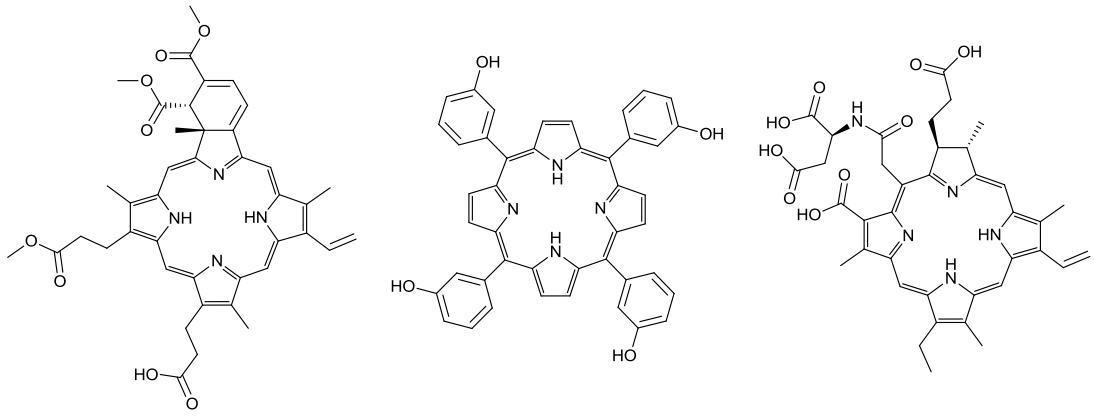
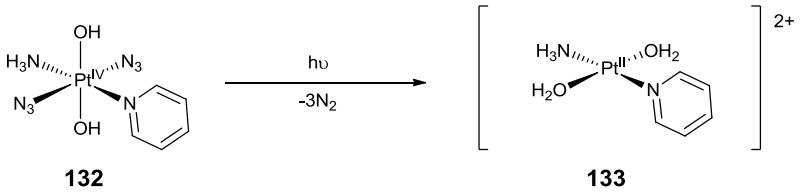


Figure 2.8. Clinically approved PDT sensitizers.[149-151]

More recently, metal-porphyrin complexes have addressed some of these restrictions with strong adsorptions at longer wavelengths (600-900 nm) and higher quantum yields. Lutetium texaphyrin is a Lu^{3+} porphyrin that is approved for PDT treatment of cervical, prostrate and brain tumours.[152] More significantly, organometallic complexes are being developed that interact directly with DNA without the need for supplementary high oxygen concentrations.[153] Photocleavage of DNA with Rh^{3+} arene complexes have been shown to weakly bind to DNA in the dark and, on excitation (320-440 nm),[154] LMCT causes a hydrogen abstraction from a deoxyribose sugar ring of the DNA ultimately causing cleavage.[155] Pt^{2+} anticancer

agents such as oxaliplatin, satraplatin and picoplatin have proven themselves as lifesaving therapeutics. However, there are problems with intrinsic resistance and general toxicity.

Pt^{4+} azide compounds **132** offer greater points of structural diversity, better aqueous solubility and lower toxicity. The area to be treated can then be irradiated with light (~400 nm) to induce a photoreduction to form aggressive Pt^{2+} complexes that are concentrated only in the locale of the affected areas (Scheme 2.2).[156]



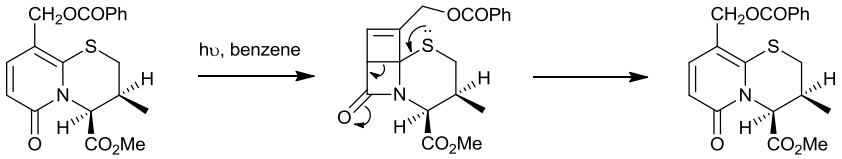
132 **133**

Scheme 2.2. Irradiation of Pt^{4+} compounds to form Pt^{2+} complexes.

In the treatment of bacterial infections, some of the same advantages of phototherapy are still applicable. Infections on the exterior of the body or those that can be easily accessed with fibre optics, such as those of skin, eyes or oral, would allow for either targeted or time delayed treatment.[157] There is also a large interest in the development of surface coatings that have antimicrobial properties for use in hospitals and other high risk areas, in order to combat the spread of life-threatening infections. Some researchers have demonstrated materials where the antimicrobial properties are continually being renewed through the action of light.[158]

Another mode of phototherapy is the photochemical interconversion of an inactive compound into a bioactive one. A relevant attempt at this has been demonstrated by Capps *et al*,[159] who used light induced electrocyclisations of 2-pyridones to make

cephalosporin derivative **135**. Unfortunately, **135** proved unstable and readily transformed back into pyridone **134**. This was postulated as being due to the sulfur appendage donating electron density into the *β*-lactam ring system, causing ring cleavage (Scheme 2.3).[160] However, small molecule prodrugs such as these remain an attractive target. Photoisomerisation of these prodrugs to biologically relevant molecules may be important in future medicinal treatments.



134 **135** **134**

Scheme 2.3. Light induced electrocyclisations by Capps *et al*.[159]

Indeed, phototherapy in general continues to be a relevant area of research, and a growing mode of treatment for a variety of ailments, especially in view of increasing antibacterial resistance.

2.2 Results and Discussion

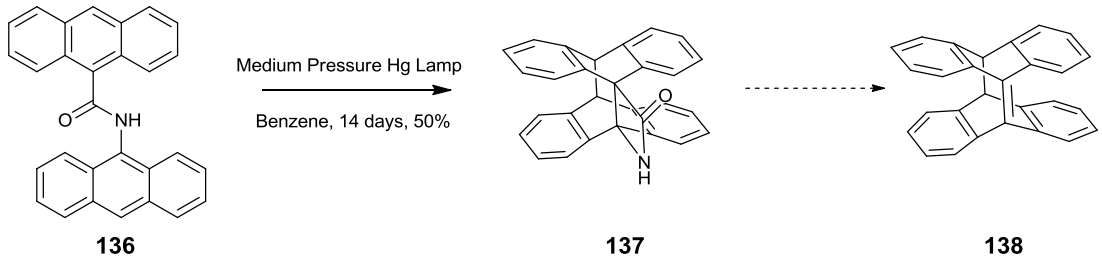
2.2.1 Introduction

In light of the prominence of *β*-lactams as antimicrobial agents, we set out to explore whether such compounds could be generated by photochemical methods, with a view to the development of novel, light-activated antimicrobial agents.

Ideally, the precursor must be highly stable, non-toxic and biologically inactive, but easily synthesised using high yielding reactions and purifications. Preferably, the precursor would readily undergo a high yielding, photochemical transformation upon irradiation with low energy visible / near visible light. This would yield a significant biological functional group, region or shape, which then gives the molecule a high level of biological activity.

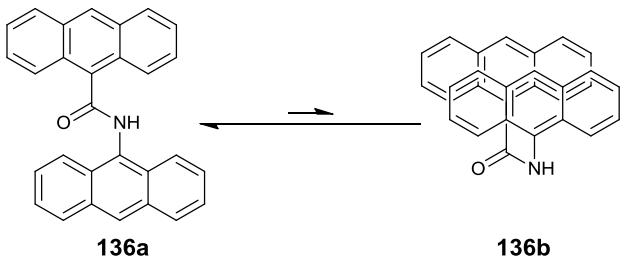
The *β*-lactam ring is a key functional group in a large and diverse family of antibiotics, which are also finding applications in other medicinal treatments. A wide range of structurally diverse *β*-lactams are known to be highly effective antimicrobial agents but, with rising levels of resistance, new and unusual structures are still relevant.[161] Additionally, there are a number of possible photochemical routes to *β*-lactams.

2.2.2 Anthracene Isomerisations



Scheme 2.4. *β*-lactam formation from the isomerisation of anthracenes.[162]

In 1968 Appelquist *et al*[162] made **137** as part of their extensive investigations focused on the development of a reliable synthesis of **138**. The formation of **137** was found to be very slow, requiring 14 days of intense irradiation to achieve a 50% yield. Presumably this was due to the rotamer populations being unfavourable for the photochemical reaction to proceed (Scheme 2.5). Whilst *β*-lactam **137** was isolated, limited data was provided and no studies of its bioactivity were reported. We reasoned that this chemistry could provide an interesting way to generate potentially new antimicrobial agents through photoactivation.



Scheme 2.5. Proposed rotamer populations.

We reasoned that it would be possible to functionalize **136** by alkylating the nitrogen with a number of substituents, which would hopefully improve solubility, enhance

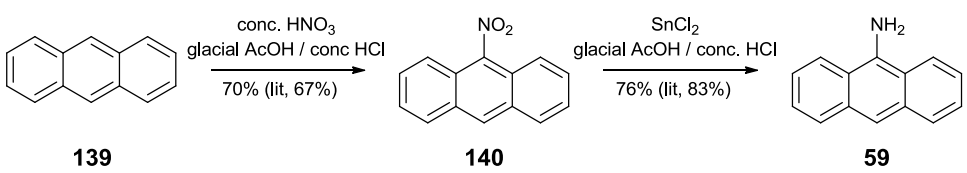
biological activity and, importantly, push the rotamer population towards the right hand side, improving the photochemical isomerisation (Scheme 2.5).

2.2.2.1 β-Lactam Synthesis

Our investigations comprised of a number of aims. Firstly, to develop a family of simply derived *β*-lactams by alkylation and photocyclisation of **136**. This family of *β*-lactams and their precursors could then be screened in biological tests against simple Gram-positive and Gram-negative bacteria. Ideally, a compound could be found that exhibits good antimicrobial activity whilst its precursor displayed little or no biological activity.

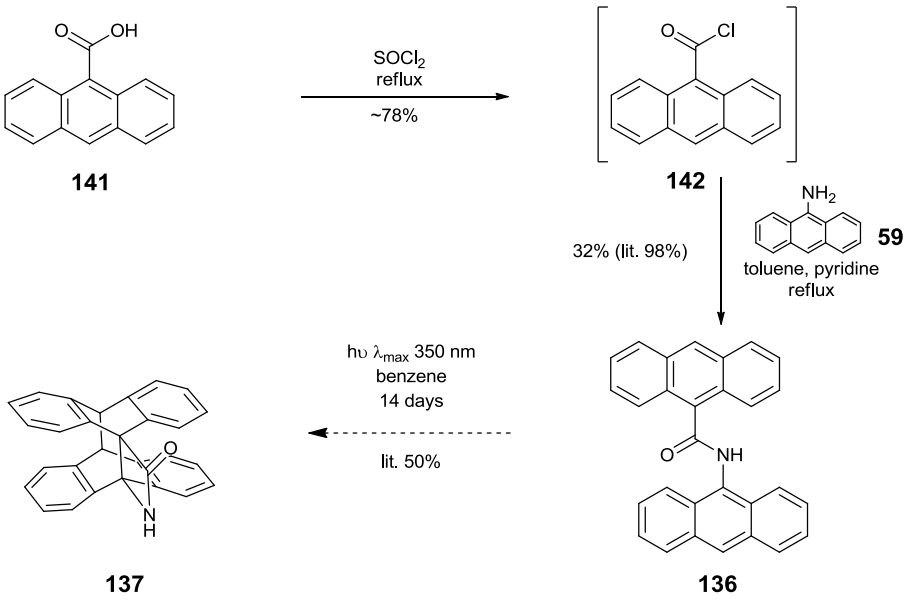
Additionally, the reaction time documented for the conversion of **136** to **137** is long and low yielding. We postulated that this was most likely due to the population of amide rotamers in the secondary amide (*vide supra)*. We hoped to establish the benefit of *N*-substitution on the propensity of the photoreaction to occur.

9-Aminoanthracene **59** was synthesised following published procedures[80] (Scheme 2.6). First, 9-nitroanthracene **140** was prepared by nitration of anthracene in 70% yield and then reduced using tin (II) chloride in concentrated hydrochloric acid to give **59** in 76% yield. 9-Aminoanthracene **59** was found to oxidize easily and required storage at −10 ^{o}C, away from sources of light.



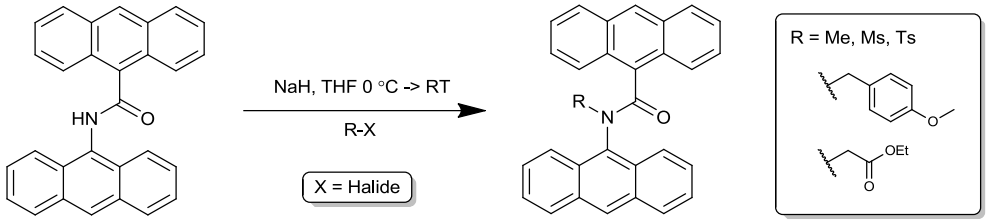
Scheme 2.6. Synthesis of 9-aminoanthracene **59**.

Carboxylic acid **141** was converted to the acid chloride **142** by refluxing in thionyl chloride, with the reaction confirmed by a shift in the C=O IR vibration from 1678 to 1779 cm^{-1}. Due to its instability, acid chloride **142** was used immediately in the next step. Acid chloride **142** was directly heated with amine **59** in toluene, in the presence of pyridine, giving amide **136** in 32% yield (Scheme 2.7). Purification of this amide by recrystallisation from benzene, as reported in the literature,[162] proved difficult due to its extremely poor solubility. More worryingly, attempts to isomerise **136** to **137** using a 125 W medium pressure Hg lamp and Pyrex filter during laboratory working hours for 5 days (lit. 14 days[162]) were completely unsuccessful, with no indication of isomerisation by ^{1}H NMR. This supports the assertion that the secondary amide is particularly difficult to isomerise due to unfavourable rotamer populations.



Scheme 2.7. Synthetic route towards **137**.

Treatment of secondary amide **136** with sodium hydride, followed by addition of an electrophile, was successful in producing a wide range of tertiary amides **143** – **147** (Table 2.1). Methylation, mesylation and tosylation were carried out with good conversions, as evidenced by crude ^{1}H NMR. Sulfonamides **144** and **145** were made because *N*-sulfur containing lactams are very effective antibiotics.[163] However, during purification of these materials, lower than expected recovery of material was obtained. In the case of mesylated compound **144**, the product was obtained cleanly but in a significantly lower yield than the crude conversion indicated. Tosylated product **145** and methylated **143** were also obtained in much lower than expected yields, however, they were also contaminated with significant quantities of isomerised products **150** and **148**. The presence of the dimerised anthracene unit was clearly indicated by the appearance of an AB system in the ^{1}H NMR spectrum around 4.6 ppm, which was not observed in the initial crude ^{1}H spectrum (Table 2.1, entries 1-3). The alkylated tertiary amides also displayed secondary signals in the ^{1}H NMR, these were determined to be rotomer signals and not isomers by noting a change in the relative integrals of these peaks in different NMR solvents for compound **152**.



Scheme 2.8. Amide substitution.

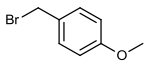
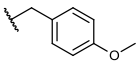
Entry	R-X	R	Yield	Compound
1	MeI	Me	Isolated*	**143**
2	MsCl	Ms	32%	**144**
3	TsCl	Ts	Isolated*	**145**
4			Not isolated‡	**146**
5			Not isolated‡	**147**

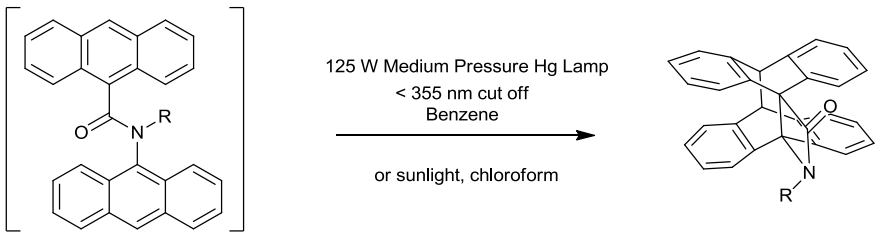
Table 2.1. Amide substitution. *Product was purified by chromatography, however further spontaneous isomerisations occurred. ‡No attempts were made to isolate these products due to spontaneous isomerisations.

Ethyl bromoacetate was used as an electrophile to provide lactam **152**. Firstly, the ester itself was an interesting target, but this compound could also be hydrolysed to give the corresponding carboxylic acid, which is a common fragment of many highly active antibiotics and might be expected to improve solubility in aqueous media. *p*-Methoxybenzyl bromide was also used as an electrophile in order to produce the related lactam **151**. This compound gave the opportunity of removing the PMB group in the final lactam, using CAN to yield the parent *β*-lactam, which we had been unable to synthesise using the reported photochemical method.

Alkylated compounds **146** and **147** were also observed to quickly isomerise in ambient conditions. Due to the low recovery of compounds **143** – **145** and because

the crude ^{1}H NMR spectroscopy data showed that the reaction was relatively clean, we decided to circumvent these problems by directly photoisomerising the alkylated products after a standard aqueous work-up.

Substituted amides **143** – **147** were much more soluble, particularly in the case of the *N*-methyl derivative. Importantly, the observed spontaneous isomerisation of the crude mixtures of **143** - **147** strongly suggested that the substitution had a direct impact on the amide rotamer populations and made the photoisomerisation much more facile, even under low energy light conditions.



Scheme 2.9. Photoisomerisation of tertiary amides.

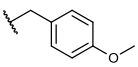
Entry	Method	R	Yield	Compound
1	A	Me	10% over 2 steps*	**148**
2	A	Ms	65%	**149**
3	A	Ts	10% over 2 steps*	**150**
4	B		37% over 2 steps	**151**
5	A		33% over 2 steps	**152**

Table 2.2. Photoisomerisation reactions. Method A: Irradiation with 125 W medium pressure Hg lamp for 1 h in benzene. Method B: a solution of the tertiary amide in chloroform was stirred in direct sunlight for 4 h. * The yield may have been significantly improved by not attempting to isolate the tertiary amide.

Initially, photoisomerisation was achieved using Method A, irradiating the sample with a 125 W medium pressure mercury lamp and quartz cooling jacket purchased from Photochemical Reactors Limited. A dilute sample of amides **143** – **145, 147** (approx. 0.0012 M) was prepared in anhydrous benzene and thoroughly degassed by freeze pump thaw under high vacuum. Anthracene photoisomerisations are very sensitive to dissolved oxygen in the solvent[164] which quickly fragments the compounds *via* the formation of anthraquinone. In order to obtain results with minimal oxidation observed, the solution had to undergo five freeze pump thaw cycles with argon being bubbled through the melted solution between cycles. The required high dilution of the reaction solution and the careful degassing made the process lengthy and limited the quantity of material that could be prepared.

To filter the broad output spectrum of the Hg lamp, we opted to use solution based filters, which allowed for greater control of the wavelengths of light that were to be filtered out, than individual multi coated glass filters. Zimmerman has reported[108] a number of highly effective, long lasting filters which can be used on their own or together to form bandpass filters. Many anthracene isomerisations are known to proceed well with irradiation at 360 nm. Higher energy irradiation can cause retro [4π + 4π] cycloaddition, degradation and oxidation. To avoid these problems, a < 355 nm cut-off filter using bismuth chloride in dilute hydrochloric acid (0.0012 M $BiCl_3$ in 2:3 conc. HCl:H_2O), as reported by Zimmerman, was optimal since transmission below 355 nm was negligible and effectively filtered out by the Pyrex reaction vessels.[111]

Method B was based on observations of how efficiently and cleanly the tertiary amides isomerised under ambient light. Crude NMR samples that were exposed to sunlight were analysed over a number of hours by ^{1}H NMR spectroscopy and indicated that the transformation was relatively fast and efficient. Importantly, even though the solvent was not degassed, there were very minimal traces of any anthracene oxidation occurring.

It was found that by dissolving the crude mixture of **146** in chloroform and exposing the stirred solution to direct sunlight under a normal atmosphere for 4 hours, the compound would isomerise almost completely with minimal oxidation. This method was found to be very effective as it completely negates the need for lengthy degassing and was not limited by solvent volumes which was a major drawback with Method A. The ability of these compounds to isomerise under these milder conditions heightened our interest, as the potential to be activated under such conditions made their medicinal use much more plausible in a similar fashion to the *in vivo* synthesis of vitamin D_3.[165]

Successful photoisomerisation of these compounds was quickly determined by the appearance of two coupled AB doublets around 4.6 ppm in the ^{1}H NMR spectrum and the disappearance of characteristic aromatic anthracene signals. The formation of a β-lactam ring was confirmed by the presence of a strong IR stretch at approximately 1745 cm^{-1}. This was supported by the x-ray crystal structure of **154** (Figure 2.9), obtained from a single crystal grown using the solvent diffusion method ($CHCl_3$, Et_2O).

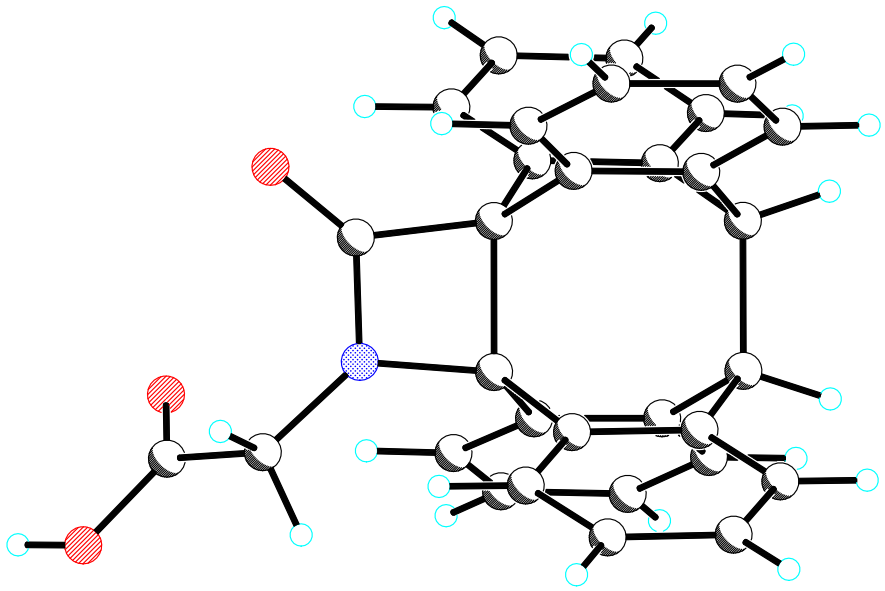
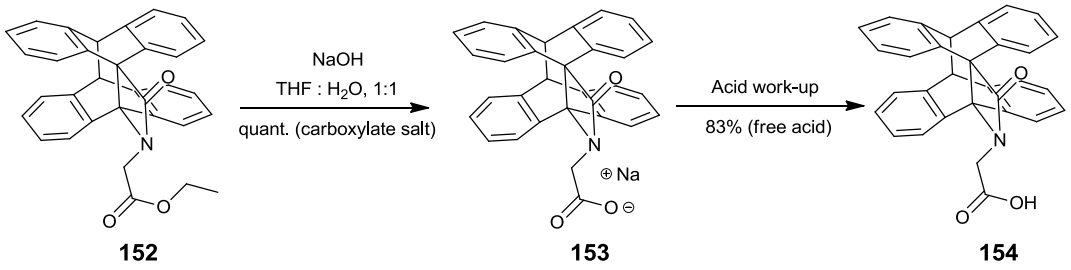


Figure 2.9. X-ray crystal structure of **154**.

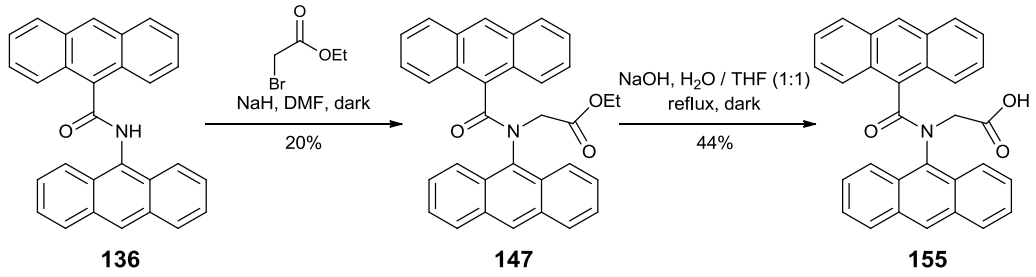
A common motif in many *β*-lactam antibiotics is an *N*-acetic acid derivative (Scheme 2.10). Treatment of **152** with sodium hydroxide in a THF / water (1:1) solution yielded the product which was initially isolated as the sodium salt **153** and used for preliminary biological testing. The free acid **154** was also prepared cleanly using an acidic aqueous work-up.



Scheme 2.10. Hydrolysis of **152**.

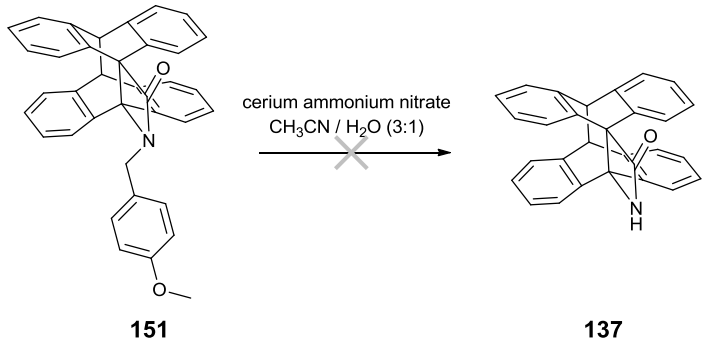
The spontaneous photoisomerisation was a welcome effect of the substitution of secondary amides **143** - **147**, and had had a much greater effect than anticipated. Unfortunately, it made the isolation of the amide precursors extremely difficult. It was necessary to isolate a clean sample of an amide precursor to validate that any

observed biological activity was solely due to the *β*-lactam and to demonstrate that an inactive compound could be converted to an active one using light. To achieve this, it was necessary to complete the synthetic and purification steps with the exclusion of ambient light. Amide **136** was alkylated and purified to form **147** using the same conditions as before but in a darkened room and isolated in 20% yield. Attempts to hydrolyse **147** using the established conditions (Scheme 2.11) were unsuccessful, but heating the reaction mixture to reflux for 6 h, followed by an acidic aqueous work-up yielded carboxylic acid **155** in 44% yield.



Scheme 2.11. Synthesis of amide precursor **155**.

Even though we had been unable to access the unsubstituted *β*-lactam **137** through the reported photochemical route, the compound was still a desirable target. Treatment of **151** with cerium ammonium nitrate, however, was not successful in removing the *p*-methoxybenzyl group (Scheme 2.12).



Scheme 2.12. Attempted alternative synthesis of **137**.

2.2.2.2 Biological Testing

Lactam **148** was the first compound tested for antimicrobial activity against two common bacteria using the Kirby-Bauer method of agar diffusion.[166] *Bacillus subtilis* was chosen as the Gram-positive bacteria and *Escherichia coli* as the Gram-negative. They are commonly reported bacteria that are easy and relatively safe to use. Ampicillin was used as a positive control as it has a high activity against both strains. Loadings of the test compound **148** (10, 50, 200 & 500 μg) were dissolved in 20 μL of dimethylsulfoxide and adsorbed onto filter pads which were then placed, along with a DMSO blank and ampicillin control, on an agar plate inoculated with each bacteria. Each experiment was carried out in duplicate and incubated overnight to allow a bacterial lawn to develop.

It was possible to clearly identify the zones of inhibition around the filter pads after bacterial lawn growth. Importantly, the DMSO control did not retard the growth of bacteria, confirming it was an acceptable solvent for the loading of the compounds. Unfortunately, there was no evidence of inhibition around any of the pads loaded with the prepared *β*-lactam **148**.

At this juncture, we decided to screen the remaining lactams **149** – **153** at the highest previous loading of 500 μg. Encouragingly, carboxylate salt **153** displayed a small zone of inhibition against *B. Subtilis* (Figure 2.10a). We were concerned that because this carboxylate salt had been used without purification (Scheme 2.10), impurities from the reaction could be providing a false positive result. To reassure ourselves that excess NaOH was not the active antibacterial agent, the impact of sodium hydroxide on the bacterial strains was investigated. Based on estimations of any

possible unreacted sodium hydroxide, loadings of 10, 50 and 100 µg were tested. At these levels sodium hydroxide was not found to affect the bacterial growth in any way.

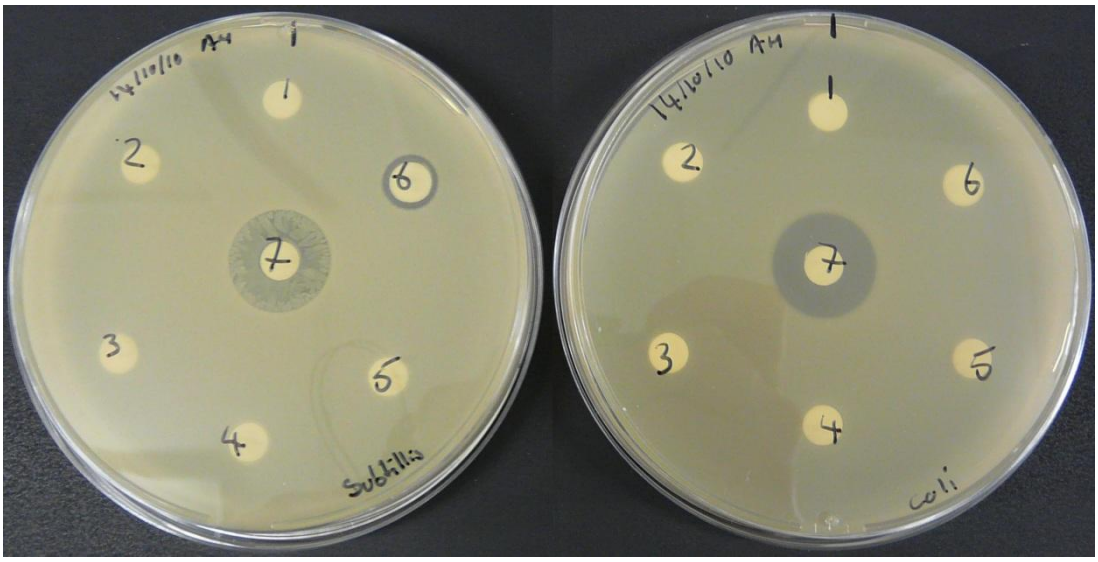


Figure 2.10a. (*B. Subtilis)* Figure 2.10b. (*E. Coli)*
Biological testing, 500 µg loading.
1 = DMSO, 2 = **150**, 3 = **149**, 4 = **152**, 5 = **151**, 6 = **153**, 7 = Ampicillin 20 µg

We wanted to test the carboxylic acid to compare its activity against the sodium salt. Compound **154** was synthesised using the same method, however, during workup, the mixture was acidified and extracted to yield the clean carboxylic acid. This acid was tested as before with loadings of 31, 63, 125, 250, 500 µg. The highest four loadings showed approximately the same zone of inhibition against Gram-positive *B. Subtilis*. The lowest loading displayed a very slight reduction in this zone (Figure 2.11a). No activity against the Gram-negative *E. Coli* was observed (Figure 2.11b).

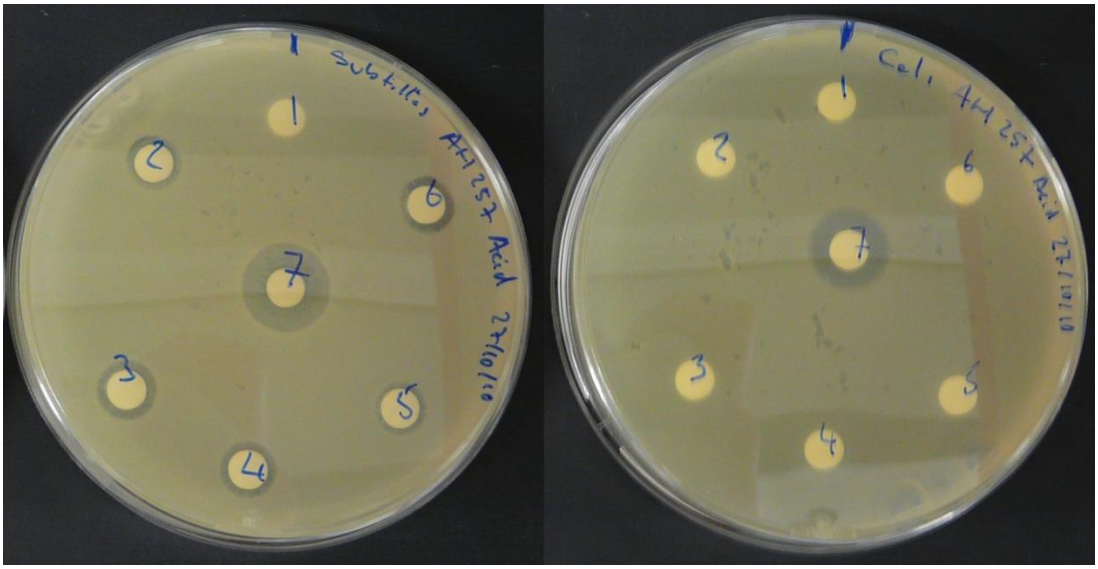


Figure 2.11a. (*B. Subtilis)* Figure 2.11b. (*E. Coli)*
Biological testing of **154**. 1 = DMSO, 2 = 31 µg, 3 = 63 µg, 4 = 125 µg, 5 = 250 µg, 6 = 500 µg, 7 = Ampicillin 20 µg

The observation that the extent of the zone of inhibition does not increase with increased concentration, suggests that diffusion in the agar media may be restricted by poor solubility.

At this juncture we had established that lactam **154** is a weak antimicrobial agent. The next step was to confirm that the *β*-lactam ring was responsible for this activity. Amide **155** was carefully prepared and purified in a dark room, to avoid contamination with *β*-lactam formed by spontaneous photoisomerisation in ambient light.

Amide **155**, along with lactam **154** as a comparison, were loaded onto agar plates inoculated with *B. Subtilis* and *E. Coli* in a dark room. Once all the plates had been loaded they were wrapped in foil to protect from light sources, and transferred to an incubator overnight. To our surprise and disappointment, amide **155** was found to be several times more active than its lactam isomer against *B. Subtilis* (Figure 2.12a)

and even displayed activity against *E. Coli* (Figure 2.12b). It therefore seems probable that the anthracene rings are important for the antimicrobial activity. Indeed, many drugs contain anthracene moieties[167] and this functional group could disrupt DNA replication by mechanisms such as intercalation.[168]

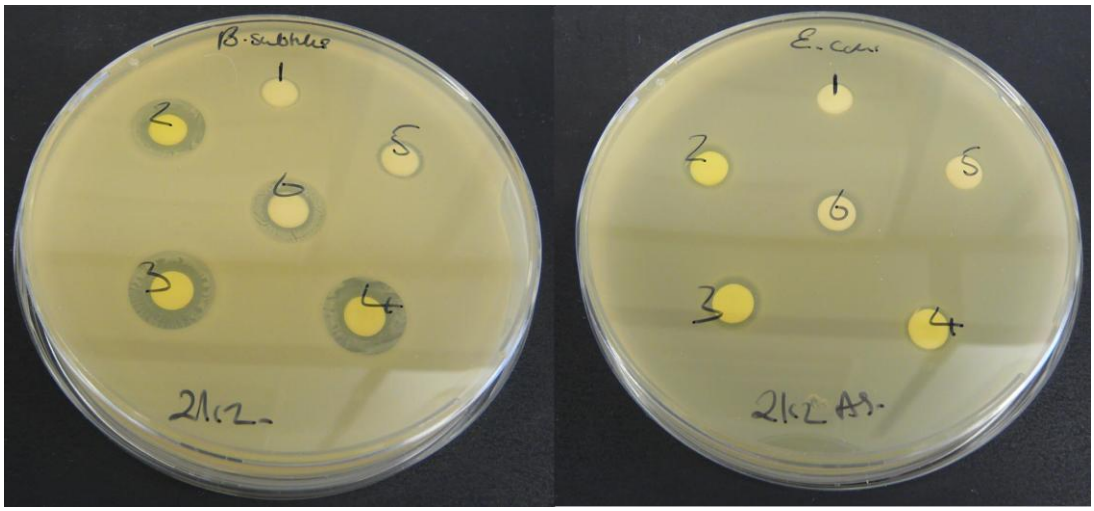


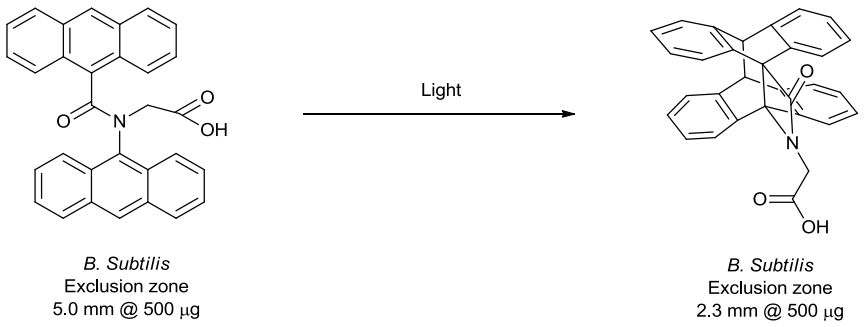
Figure 2.12a. (*B. Subtilis)* Figure 2.12b. (*E. Coli)*

Biological testing of **155**.

1 = DMSO, 2 = 60 μg, 3 = 125 μg, 4 = 500 μg, 5 = **154** 500 μg, 6 = Ampicillin 20 μg

2.2.2.3 Conclusions

By substituting the nitrogen atom of amides **143** - **147**, the rate of [4π+4π] cycloaddition has been markedly increased, reducing the reaction time from 14 days to 1 hour and allowing the reactions to proceed using low energy natural light. This cyclisation process is very clean, with little competitive oxidation of the anthracenes in deoxygenated solvent.



Scheme 2.13. Summary.

A family of tertiary amides were synthesised which were easily isomerised into highly functionalised *β*-lactams on irradiation with a UV lamp or natural sunlight, for which the structures were confirmed by x-ray crystallography. The lactams were tested for antimicrobial activity against an example of a Gram-positive (*B. Subtilis*) and Gram-negative (*E. Coli*) bacteria. Unfortunately, only compound **154** displayed a modest activity against *B. Subtilis* with the remaining compound family proving to be ineffective (Scheme 2.13).

The zone of inhibition was small but may be limited by two factors. It may be limited by poor solubility and diffusion of the compounds, which is supported by the extent of inhibition being unchanged at different compound loadings. Alternatively, the activity may be limited due to restricted reactivity of the compound. We postulate that the steric bulk of the di-anthracene rings prevents nucleophilic attack on the lactam ring, even though this ring system is highly strained (Figure 2.13). This is supported by the x-ray structure, which indicates approach at the Bürgi-Dunitz angle is blocked by the facing aromatic rings, and also by the fact that hydrolysis of the ester (Scheme 2.10) can be achieved without significant ring opening of the lactam nucleus.

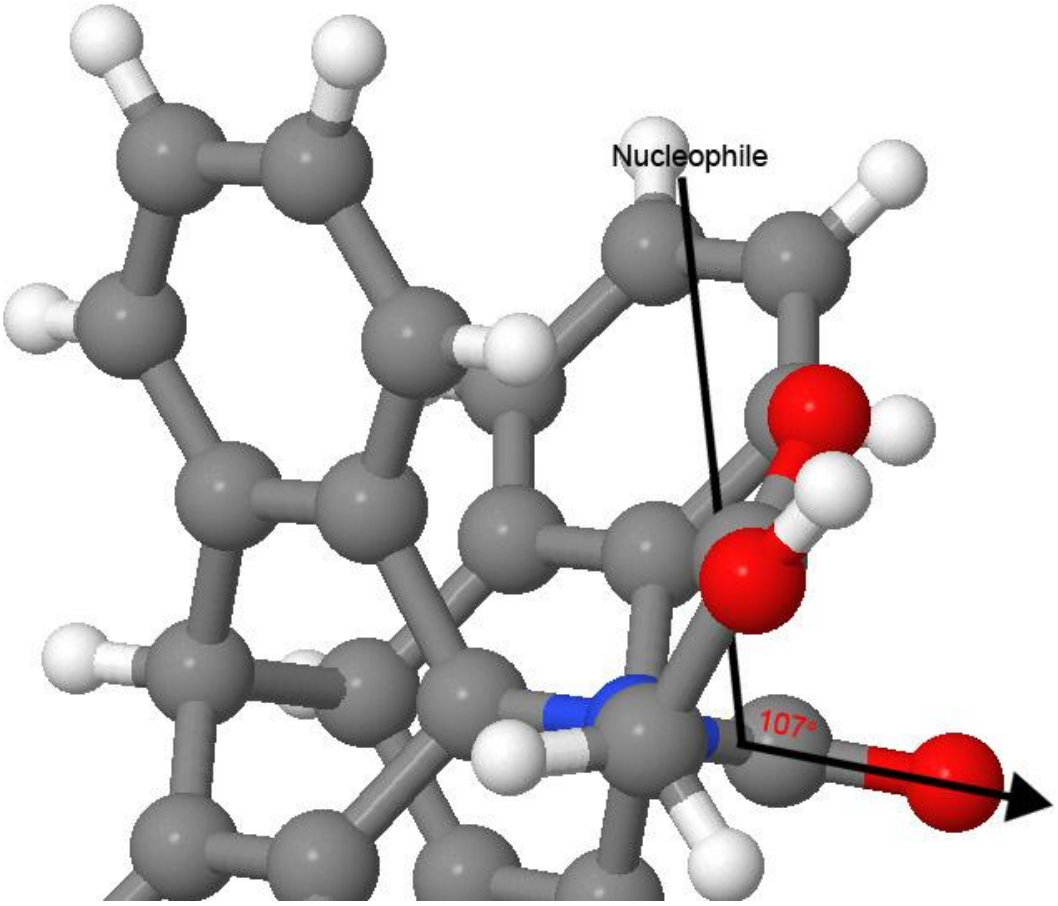
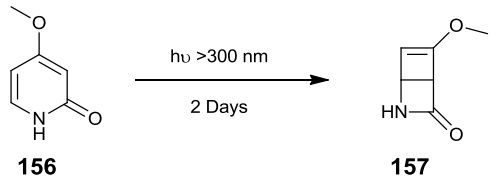


Figure 2.13. The Bürgi-Dunitz approach super-imposed on the crystal structure of **154**.

The intention was that the tertiary amide would serve as a prodrug to be converted to the active compound with light. Isolation of this compound was challenging due to a spontaneous isomerisation in ambient light, however, this was achieved in a dark room. To our consternation, when the corresponding uncyclised derivative **155** was evaluated biologically, it demonstrated considerably higher activity than lactam **154**. In view of these disappointing results we decided to explore an alternative approach based on 2-pyridones.

2.2.3 2-Pyridone Isomerisations

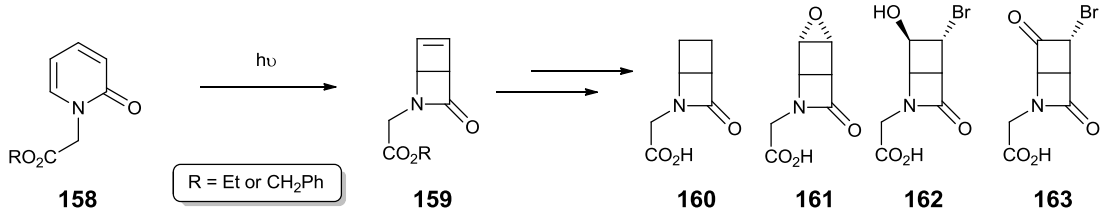
It is widely known that when 2-pyridones **156** are exposed to ultraviolet light, an isomerisation occurs to yield bicyclic *β*-lactam **157** (Scheme 2.14). In comparison to our earlier work on anthracene based systems, these lactams are less sterically crowded and, without the two anthracene rings, potentially more soluble.



156 **157**

Scheme 2.14. Photochemical isomerisation of 2-pyridones.

In section 2.2.2, we demonstrated that *β*-lactams can be synthesised through the action of light in an efficient manner. However, these anthracene based systems were hampered by poor solubility and steric overcrowding, which together hampered their ability to display useful antimicrobial activity. 2-Pyridones such as **156** are well-known for electrocyclic ring closure upon irradiation with ultraviolet light to form fused *β*-lactams. This interconversion was first demonstrated by Corey.[169] As previously noted, Capps *et al* has attempted to form *β*-lactam antibiotics in this way, focussing on lactams fused with sulfur containing rings, which are common in many commercial antibiotics such as the penicillins and cephalosporins (Scheme 2.3). Begley *et al*[170] synthesised a family of related compounds, derived from the photoisomer of *N*-benzyl-oxycarbonylmethylene-2-pyridone (Scheme 2.15). Lactams **159** – **163** were tested for biological activity against a range of Gram-positive and -negative bacteria. Unfortunately, no activity was detected for these simple derivatives.[170] However, we believed further structural diversification based on known *β*-lactam antibiotics may lead to biological activity.

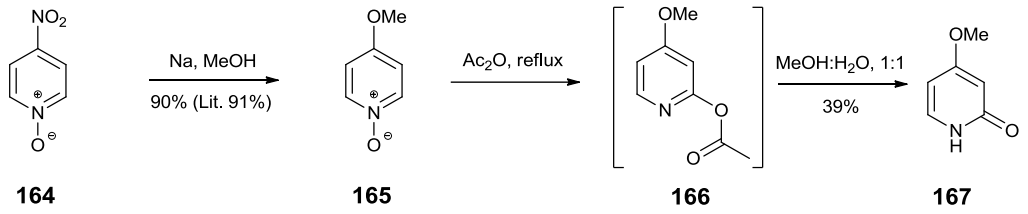


Scheme 2.15. Derivatives by Begley *et al.*[170]

We reasoned that this interconversion could provide an attractive alternative solution to the anthracene based systems. Key advantages include better solubility and increased ring strain energy that is derived from the fused bicyclic structure. Additionally, the lactam ring opening should be easier due to a less hindered nucleophilic approach, in turn leading to higher activity against bacteria. The 2-pyridone structure also offers many more sites for functionalisation to fine tune the structure in order to optimise activity.

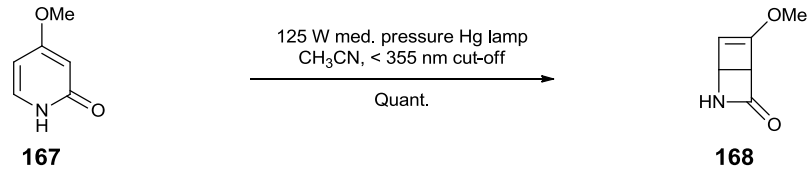
2.2.3.1 Synthesis of 2-Pyridones and Photoisomers

We started our investigations by targeting 4-methoxy-2-pyridones, as it has been reported that the 4-methoxy group greatly increases the efficiency of the photochemical isomerisation.[171] 4-Methoxypyridine-*N*-oxide **165** was synthesised by nucleophilic aromatic substitution of 4-nitropyridine-*N*-oxide in 90% yield. Isomerisation of this compound to pyridine **167** using acetic anhydride was achieved in 39% yield by first forming ester **166**, which was subsequently cleaved through stirring in methanol/water to form **167** (Scheme 2.16).



Scheme 2.16. Synthesis of **167**.

A solution of **167** in acetonitrile was degassed by freeze pump thaw cycles, then irradiated with a 125 W medium pressure Hg lamp and a bismuth chloride <355 nm cut-off filter (0.0012 M $BiCl_3$ in 2:3 conc. HCl: H_2O).[108] This isomerisation was found to be much slower than with anthracene systems **143 - 147**, and required irradiation for 24 h to achieve complete conversion to **168**. Nevertheless, the reaction was very clean with no observed side products. The isomerisation was confirmed by an upfield shift of aromatic resonances in the ^1H NMR and the appearance of a strong shift at 1740 cm^{-1} in the IR spectrum, indicative of a β-lactam ring.



Scheme 2.17. Isomerisation of **167** to **168**.

Confident that this chemistry worked well, we set out to produce a range of β-lactams that might more closely map onto the structures of known antibiotics. In this way, we hoped to make some derivatives that should possess good levels of biological activity. Nocardicin A was chosen as a basis for structural mapping as it is a naturally produced monobactam that possesses good activity against Gram-negative bacteria, notably against *Pseudomonas*[172,173] (Figure 2.14). Substitution of the 4-methoxy group with 4-benzyloxy would hopefully allow for a better structural

mapping over the 3'-6' aromatic ring of Nocardicin A. It was then hoped that alkylation of the pyridine nitrogen would lead us to a wide range of simple targets that could be tested for biological activity. The electrophiles were chosen based on previous success with the anthracene systems and common antibiotic functionality.

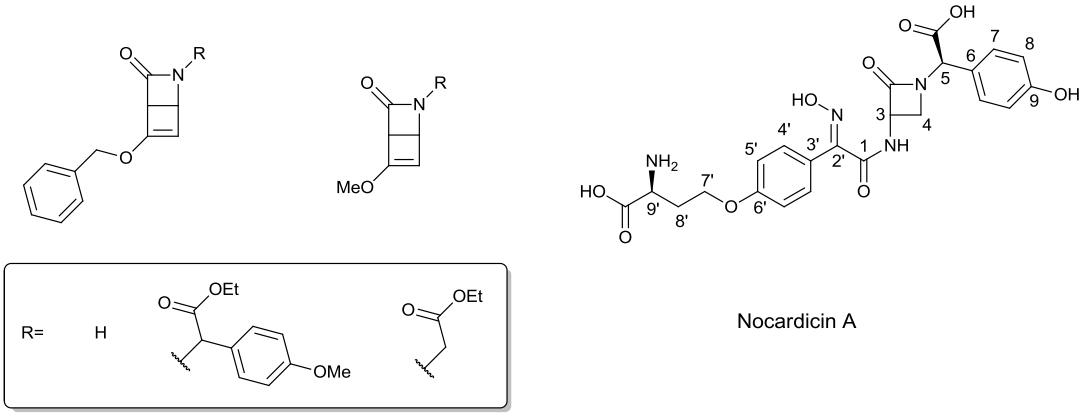
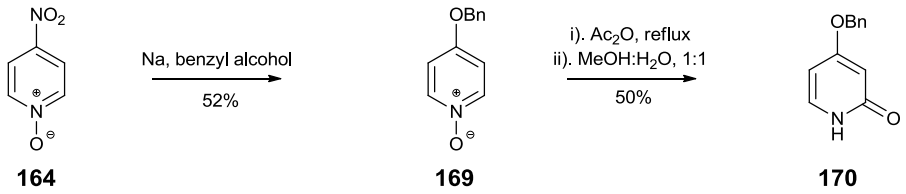


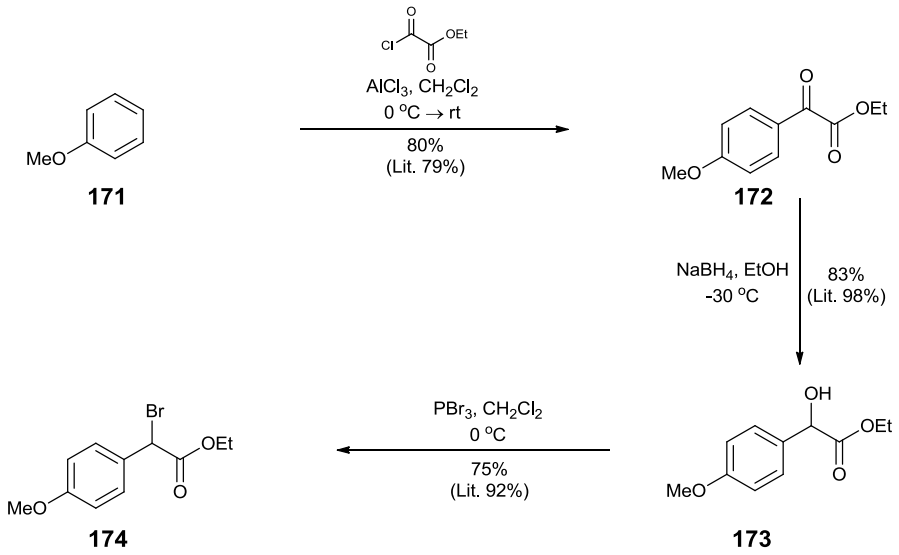
Figure 2.14. *β*-lactams based on Nocardicin A.[174]

4-Benzyloxypyridine-*N*-oxide was prepared using a modification of the earlier procedure. Benzyl alcohol was deprotonated with sodium, then reacted with 4-nitropyridine-*N*-oxide in 52% yield. The isomerisation was achieved in the same manner with acetic anhydride in an improved 50% yield (Scheme 2.18).

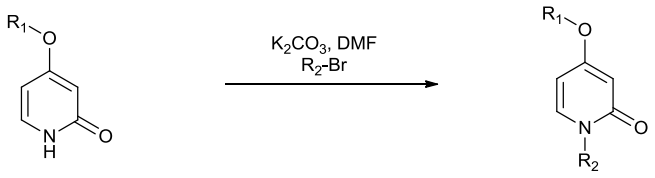


Scheme 2.18. Synthesis of **170**.

Alkylation of 2-pyridones **167** and **170** was achieved with electrophiles ethyl bromoacetate and **174**, using potassium carbonate and dimethyl formamide to give the desired products in moderate yields (Table 2.3). Electrophile **174** was prepared following a reported procedure in comparable yields (Scheme 2.19).[175] Hydrolysis of esters **175** - **176** using lithium hydroxide proved to be unsuccessful, yielding a complex mixture of products.



Scheme 2.19. Synthesis of electrophile **174**.



Scheme 2.20. Alkylation of **167** and **170**.

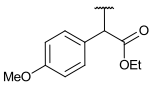
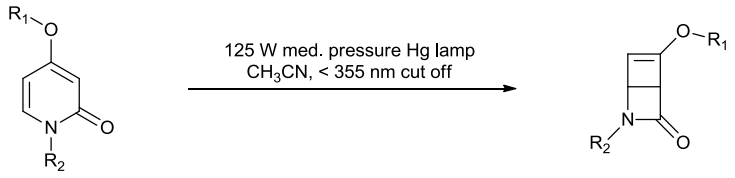
Entry	R_1	R_2	Yield	Compound
1	Me		73%	**175**
2	Bn		55%	**176**
3	Bn		53%	**177**

Table 2.3. Results for the alkylation of **167** and **170**.

Compounds **175** - **177** were irradiated using a 125 W medium pressure Hg lamp with a concentration of 1mM in acetonitrile. In the case of the NH pyridones **167** and **170**, the reaction was high yielding and very clean (Table 2.4). Pyridone **176** was successfully electrocyclised, however, significant side products were also produced, reducing the yield to 57%.

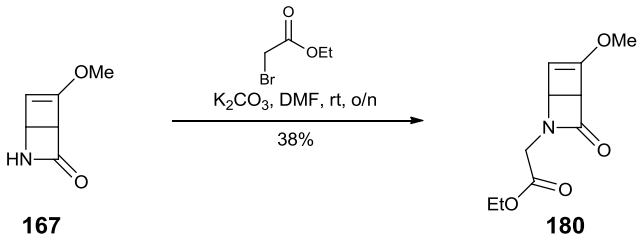


Scheme 2.21. Irradiation of 2-pyridones.

Entry	R_1	R_2	Time	Yield	Compound
1	Me	H	1 day	Quant	**168**
2	Bn	H	1 day	79%	**178**
3	Bn		2 days	57%	**179**

Table 2.4. Electrocyclisations of **167, 170** and **176**.

Substituted pyridones **175** and **177** proved more challenging as the electrocyclisation was a minor photochemical product which could not be effectively separated from the impurities. Therefore a different approach was required. As both NH pyridones isomerised cleanly, it was possible to gain access to lactam **180** *via* alkylation of the NH *β*-lactam. *β*-Lactam **167** was alkylated with ethyl bromoacetate using potassium carbonate in DMF (Scheme 2.22). The yield was moderately low (38%), but gave access to the compound for biological testing. However, repeating this reaction with electrophile **174** and lactam **170** was unsuccessful, possibly due to the increased steric crowding around the electrophilic centre.



167 **180**

Scheme 2.22. Alternative route to *β*-lactam **180**.

2.2.3.2 Biological Testing

Four lactams **168, 178** - **180** were subjected to testing against *B.Subtilis* and *E. Coli* using the Kirby Bauer test. All four compounds were loaded on to the same plate at 500 μg, along with DMSO and 20 μg ampicillin as negative and positive controls respectively.

After incubation overnight, it was clear to see that there was no zone of growth inhibition around any of the test compounds. However, there was clearly a reddish discolouration of the agar, extending in a large radius around the compounds, especially noticeable around compounds **179** and **180** (Figure 2.15). One possible explanation is that the compounds are far more soluble and diffuse much more readily than the anthracene systems. However, this most likely indicates that these compounds are too reactive and are possibly subject to destructive reactions from the aqueous agar media. This leaves two potential problems, either the compounds are ineffective antimicrobial agents or they are being rapidly deactivated before any interaction with the bacteria could occur, thereby resulting in no observed activity.

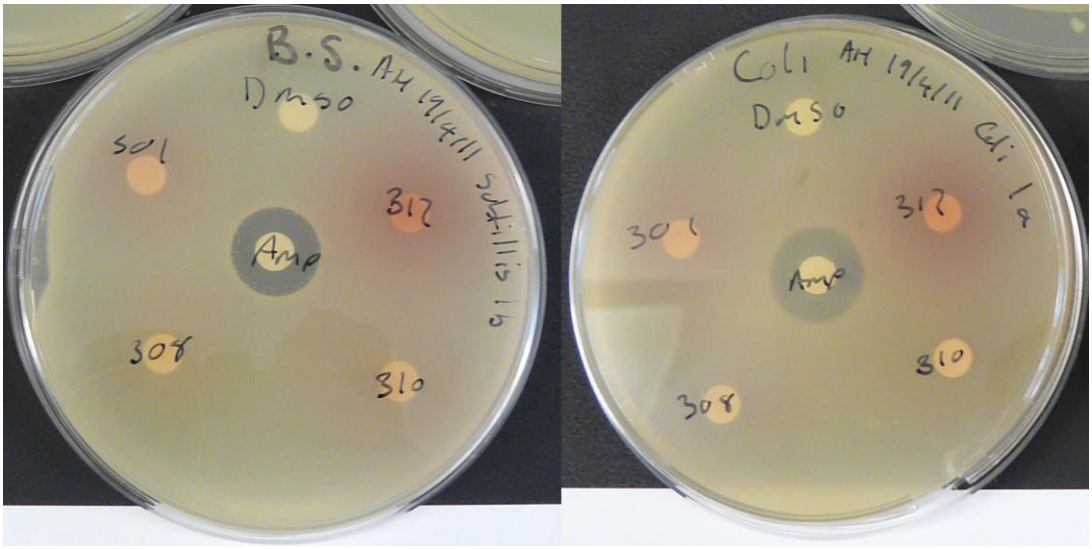


Figure 2.15a. (*B. Subtilis)* Figure 2.15b. (*E. Coli)*
Testing results of lactams 500 μg loading.
301 = **179**, 308 = **178**, 310 = **168**, 312 = **180**.

2.2.3.3 Conclusions

A small family of highly strained *β*-lactams derived from photochemical electrocyclisation of 2-pyridones were prepared. These compounds addressed our concerns regarding poor solubility, diffusion and hindered nucleophilic approach vectors. The lactam interconversion was very clean and effective with the NH pyridones, but more challenging with *N*-alkylated pyridones as the efficiency of the photochemical reaction dropped markedly.

Unfortunately none of the tested compounds (**168, 178** – **180**) were found to have any antimicrobial activity. This may be a result of being too reactive, as high ring strain energy may make the *β*-lactam ring very prone to nucleophilic opening. Alternatively, these compounds may not be compatible treatments for the selected bacteria, and more encouraging results may be encountered by screening against a

broader spectrum of bacteria, or through further modification of the pyridone substituents to enhance binding to the penicillin binding protein.

Chapter 3:

Experimental

3.1 General Procedures

All reactions were performed under an atmosphere of dry nitrogen or argon in flame or oven dried glassware unless otherwise stated. Anhydrous solvents were purchased from Sigma-Aldrich or Fisher Scientific in Sure-Seal™ bottles for use as reaction solvents. All other solvents were reagent grade, used as received or purified by standard protocols where stated. Petrol refers to the petroleum ether fraction which boils in the range 40-60 ^{o}C for column chromatography or 60-80 ^{o}C for recrystallisations.

Commercially available starting materials were used without further purification unless otherwise stated. Thin layer chromatography was performed on pre-coated aluminium-backed plates (Merck Silicagel 60 F254), visualised by UV 254 nm then stained with potassium permanganate or ceric ammonium molybdate solution. Flash chromatography was performed using Matrex silica 60. Melting points were recorded on a Gallenkamp MPD350 apparatus and are reported as observed. Single crystal X-ray diffraction data were obtained using a Siemens SMART XRD system or an Oxford Diffraction Gemini XRD system.

Nuclear magnetic resonance (NMR) spectra were recorded on Bruker DPX (300, 400, 500 or 600 MHz) spectrometers. VT NMR measurements were performed on a 500 or 600 MHz spectrometer. Chemical shifts are reported in parts per million relative to the standard tetramethylsilane. The peak multiplicities were specified as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint). Coupling constants (J) are reported in Hertz.

Low resolution mass spectra were recorded on an Esquire 2000 platform with electrospray ionisation. High resolution mass spectra were obtained using a Bruker MicroTOF spectrometer.

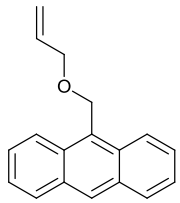
3.1.1 Photochemical Procedures

All experiments carried out using a laboratory light source were done using equipment purchased from Photochemical Reactors Ltd (Berkshire, UK). The lamp used was a 125 W medium pressure mercury, high intensity discharge lamp (model: 3010) supported by a 125 W power supply (Model: 3110). The lamp was cooled using an immersion quartz water jacket (Model: 3210).

A variety of experimental setups and filters were used, which are detailed in Appendix 2.

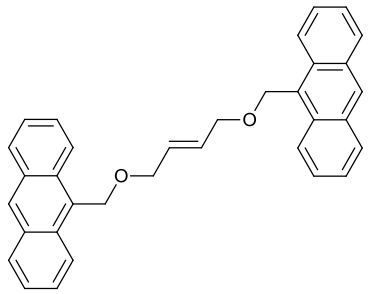
3.2 Control of Molecular Motion Experimental

9-Allyloxymethyl-anthracene (33)



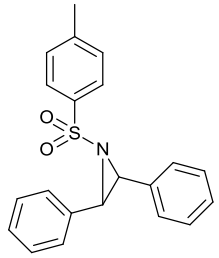
A known compound[59] synthesized using a modified reported procedure.[176] A solution of anthracene-9-yl methanol (1.00 g, 4.80 mmol, 1.0 eq) in dry DMF (10 mL) was placed under nitrogen, stirred and cooled to 0 ^{o}C. Sodium hydride (60% in mineral oil, 210 mg, 5.30 mmol, 1.1 eq) was then added, followed by allyl bromide (580 mg, 4.80 mmol, 1.0 eq) added dropwise. The resulting mixture was stirred for 1 h at 0 ^{o}C then allowed to warm and stirred for 1 h at room temperature. The reaction was then quenched with water (30 mL) and extracted with EtOAc (3 x 20 mL). The combined organics were washed with water (2 x 10 mL), sodium bicarbonate (10 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The yellow solid was purified by flash chromatography (3% EtOAc in petrol), then recrystallised (petrol) to give **33** as light yellow crystals (594 mg, 50%). R_f = 0.47 (5% EtOAc in petrol); m.p. = 65 – 67 ^{o}C (petrol); IR (thin film) 2871, 1677, 1644, 1622, 1592, 1523, 1126, 727 cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$) δ 4.17 (2H, d, *J* = 5.8, OC*H*$_2$), 5.24 (1H, dd, *J* = 10.4, 1.3, CH=C*H*H), 5.35 (1H, dd, *J* = 17.3, 1.3, CH=CH*H*), 5.44 (2H, s, ArC*H*$_2$O), 5.96 - 6.07 (1H, m, C*H*=CH$_2$), 7.42 (2H, dd, *J* = 8.8, 7.4, Ar*H*), 7.51 (2H, dd, *J* = 8.4, 7.4, Ar*H*), 7.97 (2H, d, *J* = 8.4, Ar*H*), 8.36 (2H, d, *J* = 8.8, Ar*H*), 8.41 (1H, s, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 64.2 (CH_2), 71.5 (CH_2), 117.7 (CH_2), 124.4 (CH), 125.0 (CH), 126.2 (CH), 128.4 (CH), 128.8 (C), 129.1 (CH), 131.1 (C), 131.5 (C), 135.0 (CH).

(2*E*) and(2*Z*)-1,4-Bis(9-anthryloxy)but-2-ene (34)



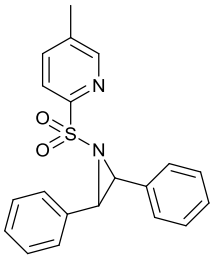
A novel compound synthesized using a modified procedure.[177] Dry dichloromethane (8 mL) was deoxygenated by repeated freeze pump thaw cycles under nitrogen, and transferred to a flask containing 9-allyloxymethyl-anthracene (400 mg, 1.60 mmol, 1.0 eq) *via* cannula. Grubbs I catalyst (66 mg, 8.02 x 10^{-5} mol, 5 mol%) was added and the solution slowly warmed to 50 ^{o}C so that the oil bath temperature did not exceed 60 ^{o}C. After 5 h the solution was concentrated *in vacuo* yielding a dark brown oil. Purification by flash chromatography (10% EtOAc in petrol) produced a light brown solid which was recrystallised (50% EtOAc in petrol), yielding small beige crystals (238 mg, 59%) as a 3:1 inseperable mixture of *trans* and *cis* isomers. m.p. 106-108 ^{o}C (50% EtOAc in petrol); R_f = 0.24 (10% EtOAc in petrol); IR (thin film) 2868, 1674, 1647, 1590, 1526, 1118, 727 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ major: 4.21 - 4.23 (4H, m, OC*H*$_2$), 5.47 (4H, s, ArC*H*$_2$), 5.97 - 6.01 (2H, m, =C*H*), 7.42 – 7.52 (8H, m, Ar*H*), 7.99 (4H, d, *J* = 8.0, Ar*H*), 8.37 (4H, d, *J* = 8.7, Ar*H*), 8.45 (2H, s, Ar*H*); minor: 4.21 - 4.23 (4H, m, OC*H*$_2$), 5.37 (4H, s, ArC*H*$_2$), 5.90 (2H, br t, *J* = 3.9, =C*H*), 7.42 – 7.52 (8H, m, Ar*H*), 7.99 (4H, d, *J* = 8.0, Ar*H*), 8.31 (4H, d, *J* = 8.7, Ar*H*), 8.45 (2H, s, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 64.3 (CH_2), 66.0 (CH_2), 70.4 (CH_2), 124.3 (CH), 124.4 (CH), 125.0 (CH), 126.2 (CH), 128.4 (CH), 129.0 (CH), 130.1 (CH), 128.7 (C), 131.0 (C), 131.5 (C); MS (ES^+) *m/z* 469 $[M+H]^+$; HRMS (ES^+) calcd for $C_{34}H_{29}O_2$, 469.2959 $[M+H^+]$, found 469.2955.

(2*S, 3*S**)-2,3-Diphenyl-1-(toluene-4-sulfonyl)-aziridine (181)**



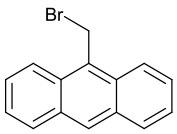
A known compound synthesized using a reported procedure.[62] To a solution of *trans*-stilbene (965 mg, 5.35 mmol, 5.0 eq) in dichloromethane (5 mL) was added PhINTs (400 mg, 1.07 mmol, 1.0 eq). $Cu(acac)_2$ (28 mg, 0.1 mmol, 10 mol%) was added forming a dark green mixture. This was stirred for 3 h under nitrogen until all of the suspended PhINTs had been dissolved. The solution was then filtered through a plug of celite which was washed with dichloromethane and concentrated *in vacuo*. Purification by flash chromatography (10 – 20% EtOAc in petrol) furnished a white solid. This solid was recrystallised (50% EtOAc in petrol) to give **81** as fluffy white crystals (135 mg, 36%). R_f = 0.24 (10% EtOAc in petrol); ^{1}H NMR ($CDCl_3$, 400MHz) δ 2.38 (3H, s, C*H*$_3$), 4.26 (2H, s, C*H*), 7.20 (2H, d, *J* = 8.2, TsAr*H*), 7.31 - 7.38 (6H, m, Ar*H*), 7.39 - 7.44 (4H, m, Ar*H*), 7.62 (2H, d, *J* = 8.2, TsAr*H*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.6 (CH_3), 50.4 (CH), 127.6 (CH), 128.3 (CH), 128.5 (CH), 128.7 (CH), 129.4 (CH), 133.1 (C), 137.1 (C), 142.0 (C); MS (ES^+) *m/z* 350 [$M+H^+$], 372 [$M+Na^+$].

(2*S, 3*S**)-*2*-(2,3-Diphenyl-aziridine-1-sulfonyl)-5-methyl-pyridine (36)**



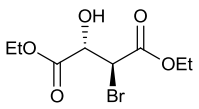
A novel compound synthesized using a modified procedure.[65] dichloromethane (1 mL) was added to a flask containing 4 Å powdered molecular sieves (500 mg), *trans* stilbene (108 mg, 0.60 mmol, 1.2 eq), iodobenzene diacetate (161 mg, 0.50 mmol, 1.0 eq), 5-methyl-2-pyridinesulfonamide (86 mg, 0.50 mmol, 1.0 eq) and $Cu(acac)_2$ (7 mg, 0.025 mmol, 5 mol%) and the mixture stirred for 20 h at room temperature. The resulting light green mixture was filtered through a plug of celite and washed with dichloromethane then concentrated *in vacuo*. Purification by flash chromatography (25 – 30% EtOAc in petrol) yielded **36** as a white powder (62 mg, 36%). m.p. 148-149 ^{o}C (powder 25 – 30% EtOAc in petrol); R_f = 0.14 (30% EtOAc in petrol); IR (thin film) 3034, 1571, 1450, 1319, 1168, 902, 765, 688 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.38 (3H, s, C*H*$_3$), 4.42 (2H, s, NC*H*), 7.28 - 7.38 (6H, m, Ar*H*), 7.43 - 7.49 (4H, m, Ar*H*), 7.51 (1H, d, *J* = 8.0, Py*H*), 7.62 (1H, d, *J* = 8.0, Py*H*), 8.48 (1H, s, Py*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.6 (CH_3), 50.7 (CH), 122.0 (CH), 128.3 (CH), 128.5 (CH), 128.7 (CH), 133.1 (CH), 137.5 (C), 137.9 (C), 150.4 (CH), 154.6 (C); MS (ES^+) *m/z* 351 [$M+H^+$]; HRMS (ES^+) calcd. for $C_{20}H_{18}N_2O_2NaS$, 373.0981 [$M+Na^+$], found 373.0990; Anal. Calcd. For $C_{20}H_{18}N_2O_2S$: C, 68.55; H, 5.18; N, 7.99; S, 9.15%. Found: C, 68.63; H, 5.20; N, 7.92; S, 9.01%.

9-Bromomethylanthracene (182)



A known compound synthesized using a reported procedure.[178] A suspension of anthracene-9-yl methanol (1.00 g, 4.80 mmol, 1.0 eq) was dissolved in toluene (26 mL) and cooled to 0 ^{o}C, PBr_3 (761 mg, 2.80 mmol, 1.2 eq) was then added dropwise *via* syringe. The solution was stirred for 1 h at 0 ^{o}C then warmed to room temperature. Saturated Na_2CO_3 solution (5 mL) was added slowly and the mixture allowed to return to room temperature. The organic phase was separated and washed with water (4 mL), brine (4 mL) then dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was recrystallised (50% EtOAc in petrol), yielding **182** as yellow needle-like crystals (560 mg, 86%). R_f = 0.16 (10% EtOAc in petrol); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.52 (2H, s, C*H*$_2$), 7.50 (2H, dd, *J* = 8.9, 7.5, Ar*H*), 7.63 (2H, dd, *J* = 8.4, 7.5, Ar*H*), 8.03 (2H, d, *J* = 8.4, Ar*H*), 8.30 (2H, d, *J* = 8.9, Ar*H*), 8.47 (1H, s, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.0 (CH_2), 123.5 (CH), 125.4 (CH), 126.8 (CH), 127.9 (C), 129.22 (C), 129.3 (CH), 129.7 (CH), 131.6 (C).

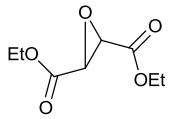
Diethyl (2*S*,3*S*)-2-bromo-3-hydroxysuccinate (38)



A known compound synthesized using a reported procedure.[66] A solution of 40% HBr in acetic acid (100 mL) was added dropwise to stirred diethyl-L tartrate (26.0 g, 0.126 mol, 1.0 eq) at 0 ^{o}C over 30 minutes. The solution was stirred for a further 15 minutes at 0 ^{o}C then allowed to warm to room temperature and stirred for 10 h. The reaction mixture was then poured into ice (500 g) and transferred to a 1 L separating funnel. The mixture was extracted with diethyl

ether (4 x 80 mL) and the combined organics washed with water (3 x 60 mL), brine (100 mL), dried ($MgSO_4$) then concentrated *in vacuo* to a yellow / orange oil. To this oil was added ethanol (140 mL) and the flask equipped with a condenser capped with a silica containing drying tube. Acetyl chloride (4.42 g, 56.3 mmol) was carefully added and the solution heated to reflux for 7 h, then concentrated *in vacuo*. The crude product was purified by vacuum distillation (120 ^oC, 4 mbar) yielding **38** as a very pale yellow oil (26.7 g, 79%). ^1H NMR (400 MHz, $CDCl_3$) δ 1.30 (6H, t, *J* = 7.1, C*H*$_3$), 4.19 - 4.31 (4H, m, C*H*$_2$), 4.65 (1H, d, *J* = 4.1, C*H*), 4.70 (1H, d, *J* = 4.3, C*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7 (CH_3), 13.8 (CH_3), 47.5 (CH), 62.3 (CH_2), 62.6 (CH_2), 72.4 (CH), 166.5 (C=O), 170.1 (C=O); MS (ES^+) *m/z* 269 [^{79}BrM+H]$^+$, 271 [^{81}BrM+H]$^+$, 291 [^{79}BrM+Na]$^+$, 293 [^{81}BrM+Na]$^+$.

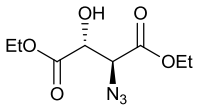
Diethyl (2*R*, 3*R*)-2,3-epoxysuccinate (39)



A known compound synthesized using a reported procedure.[66] A solution of sodium ethoxide was prepared by addition of sodium (2.99 g, 130 mmol, 1.3 eq) to dry ethanol (11 mL). This solution was then added by means of a large bore cannula to a solution of **38** (26.7 g, 99.0 mmol, 1 eq) in dry ethanol (72 mL) at 0 ^oC over a period of 2 h. Following addition, the solution was stirred for a further 30 minutes then quenched by the addition of acetic acid (1.43 mL). The solution was diluted with water (450 mL) and extracted with dichloromethane (4 x 50 mL). The combined organics were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The pale yellow crude oil was purified by vacuum distillation (89 ^oC, 1 mbar) yielding **39** as a highly mobile, colourless oil (13.2 g, 71%). R_f = 0.6 (20% EtOAc in petrol); IR (thin film) 2984,

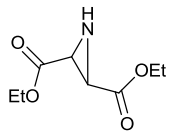
1737, 1467, 1446, 1370, 1327, 1276, 1192, 1094, 1024 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (6H, t, *J* = 7.2, C*H*$_3$), 3.67 (2H, s, NC*H*), 4.21 - 4.29 (4H, m, C*H*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) 13.9 (CH_3), 51.9 (CH), 62.1 (CH_2), 166.7 (C=O).

Diethyl (2*S*, 3*R*)-2-azido-3-hydroxysuccinate (40)



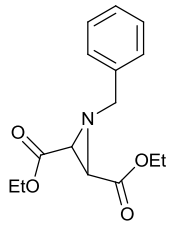
A known compound synthesized using a reported procedure.[66] To a solution of DMAP (584 mg, 4.80 mmol, 0.3 eq) in dry DMF (3 mL), was added dry ethanol (0.33 mL, 5.6 mmol). The resulting mixture was stirred and cooled to 0 ^{o}C before azidotrimethylsilane (2.39 g, 21.0 mmol, 1.3 eq) was added dropwise *via* syringe. The resulting homogeneous mixture was allowed to warm to room temperature and stirred for an additional 15 minutes. A solution of **39** (3.00 g, 16.0 mmol, 1.0 eq) in dry chloroform (8.4 mL) was added rapidly by syringe and stirred for 30 h at room temperature. The cooled mixture was diluted with water (60 mL) and extracted with 1:1 hexane:ether (4 x 12 mL), dried ($MgSO_4$) then added to a solution of hydrogen chloride in ethanol (6 mL, 2.3 N solution) and stirred for 30 minutes. The mixture was washed with water (4 x 2 mL), sodium bicarbonate (2 mL) and brine (2 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give **40** as a pale yellow oil which was used without further purification (3.01 g, 81%). IR (thin film) 3482, 2115, 1737 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (3H, t, *J* = 7.2, C*H*$_3$), 1.32 (3H, t, *J* = 7.2, C*H*$_3$), 3.26 (1H, d, *J* = 5.5, C*H*), 4.18 - 4.33 (4H, m, C*H*$_2$), 4.63 (1H, dd, *J* = 5.5, 2.7, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.21(CH_3), 14.24 (CH_3), 62.4 (CH), 62.8 (CH_2) 64.5 (CH_2), 72.0 (CH), 168.9 (C=O), 170.9 (C=O).

(2*S*, 3*S*)-Aziridine-2,3-dicarboxylic acid diethyl ester (41)



A known compound synthesized using a reported procedure.[67] To a solution of **40** (5.60 g, 24.0 mmol, 1.0 eq) in DMF (93 mL) at 0 ^{o}C, was slowly added PPh_3 (6.40 g, 24.0 mmol, 1.0 eq) portion wise. This solution was stirred at room temperature for 1.5 h then heated to 100 ^{o}C overnight. The crude mixture was diluted with water (10 mL) and extracted with EtOAc (4 x 5 mL). The organic extracts were combined and washed with water (6 x 5 mL) and brine (5ml) then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (20 – 30% EtOAc in petrol) yielded **41** as a pale yellow oil (2.42 g, 60%). R_f = 0.22 (20% EtOAc in petrol); IR (thin film) 2983, 1724, 1446, 1336, 1258, 1179, 1030, 746 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (6H, t, *J* = 7.1, C*H*$_3$), 1.78 (1H, s, N*H*), 2.85 (2H, s, NC*H*), 4.16 – 4.28 (4H, m, C*H*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9 (CH_3), 35.1 (CH), 36.0 (CH), 61.4 (CH_2), 62.0 (CH_2), 168.6 (C=O), 170.3 (C=O); MS (ES^+) *m/z* 188 [$M+H^+$].

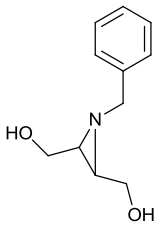
(2*S*, 3*S*)-1-Benzyl-aziridine-2,3-dicarboxylic acid diethyl ester (42)



A known compound synthesised using a reported procedure.[67] To a solution of **41** (644 mg, 3.40 mmol, 1.0 eq) in dry acetonitrile (5 mL) was added potassium carbonate (952 mg, 6.90 mmol, 2.0 eq) and 18-crown-6 (10 mg, 10 mol%). The solution was stirred at 0 ^{o}C and benzyl bromide (589 mg, 3.40 mmol, 1.0 eq) was added dropwise and the solution heated to 50 ^{o}C for 24 h. The solution was cooled and additional benzyl bromide (471 mg, 2.80 mmol, 0.8 eq) added dropwise. The solution was again heated to

50 ^{o}C for 24 h. The salts were removed by filtration and the solution concentrated *in vacuo*. The crude yellow oil was purified by flash chromatography (5 – 10% EtOAc in petrol) to give **42** as a very pale yellow oil (658 mg, 70%). R_f = 0.69 (20% EtOAc in petrol); IR (thin film) 2979, 1726, 1496, 1454, 1179, 736, 695 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (3H, m, C*H*$_3$), 1.29 (3H, m, C*H*$_3$), 3.00 (1H, br s, NC*H*), 3.13 (1H, br s, NC*H*), 4.00 (1H, d, *J* = 13.8, NCH*H*), 4.15 – 4.24 (4H, m, C*H*$_2$), 4.20 (1H, d, *J* = 13.8, NC*H*H), 7.25 – 7.38 (5H, m, Ar*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1 (CH_3), 41.1 (CH_3), 44.2 (CH), 54.7 (NCH_2), 61.6 (CH_2), 127.2 (CH), 128.1 (CH), 128.2 (CH), 138.4 (C), 167.3 (C=O), 169.0 (C=O); MS (ES$^+$) *m/z* 278 [M+H$^+$].

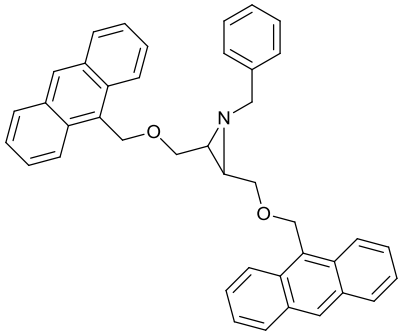
(2*S*, 3*S*)-(1-Benzyl-3-hydroxymethyl-aziridin-2-yl)-methanol (43)



A known compound synthesised using a reported procedure.[67] Lithium aluminium hydride (1.00 g, 26.2 mmol, 8.0 eq) was suspended in THF (28 mL) and cooled to -10 ^{o}C. A solution of **42** (908 mg, 3.28 mmol, 1.0 eq) in THF (6.4 mL) was added dropwise *via* syringe and the mixture stirred at -10 ^{o}C for 4 h. EtOAc (10 mL) was carefully added, followed by 50% EtOAc in water (20 mL). The resulting gel was carefully washed with EtOAc and the filtrate dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (5% MeOH in dichloromethane) gave **43** as a white solid (378 mg, 60%). R_f = 0.09 (5% MeOH in dichloromethane); ^{1}H NMR (400 MHz, MeOD) δ 2.03 (1H, m, NC*H*), 2.25 (1H, dt, *J* = 7.4, 3.7, NC*H*), 3.51 (1H, dd, *J* = 11.7, 5.5, CH*H*), 3.56 (1H, dd, *J* = 11.7, 5.8, C*H*H), 3.63 (1H, d, *J* = 13.7, NCH*H*), 3.88 (1H, dd, *J* = 12.6, 7.8, CH*H*), 4.00 (1H, dd, *J* = 12.6, 3.9, C*H*H), 4.02 (1H, d, *J* = 13.7, NC*H*H), 7.28 (1H, t, *J* = 7.3, Ar*H*), 7.36 (2H, t, *J* = 7.4, Ar*H*), 7.45 (2H, d, *J* = 7.2,

Ar*H*); ^{13}C NMR (100 MHz, MeOD) δ 43.6 (CH), 45.7 (CH), 56.0 (CH_2Ph), 59.1 (CH_2OH), 64.3 (CH_2OH), 128.2 (CH), 129.3 (CH), 129.5 (CH), 140.7 (C); MS (ES^+) *m/z* 194 [$M+H^+$].

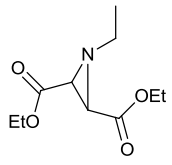
(2*S*, 3*S*)-2,3-*Bis*-(anthracen-9-ylmethoxymethyl)-1-benzyl-aziridine (44)



A novel compound synthesised using a standard alkylation procedure. 60% sodium hydride in mineral oil (22 mg, 0.54 mmol, 2.2 eq) was washed with dry *n*-pentane (2 x 1 mL) and dried under vacuum. Dry DMF (0.4 mL) was added, followed by 15- crown-5 (6 mg, 10 mol%) and the suspension cooled to 0 ^{o}C. A 0 ^{o}C solution of **43** (50 mg, 0.25 mmol, 1.0 eq) in DMF (0.4 mL) was added dropwise *via* syringe and the mixture stirred at 0 ^{o}C for 30 minutes. Then a solution of 9-(bromomethyl)anthracene (155 mL, 0.57 mmol, 2.3 eq) in DMF (0.4 mL) was added dropwise, before the mixture was allowed to warm to room temperature and stirred for 2 days. The reaction mixture was quenched with water (5 mL) and extracted with EtOAc (2 mL). An emulsion formed during extraction so the mixture was diluted with brine (10 mL), then extracted with EtOAc (4 x 5 mL). The combined organic extracts were washed with water (6 x 2 mL), brine (2 mL) dried ($MgSO_4$), then concentrated *in vacuo* to give a light yellow solid. Purification by flash chromatography (20 – 30% EtOAc in petrol), followed by further flash chromatography (10% Acetone, 10% diethyl ether in petrol) yielded **44** as a light green/yellow solid (721 mg, 48%). m.p. 140 ^{o}C (dec); R_f = 0.08 (30% EtOAc in petrol); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.74 - 1.79 (1H, m, NC*H*), 2.18 - 2.24 (1H,

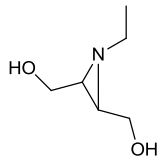
m, NC*H*), 3.23 (1H, d, *J* = 14.0, NCH*H*), 3.51 (1H, dd, *J* = 10.6, 5.1, CHCH*H*O), 3.57 (1H, dd, *J* = 10.6, 5.9, CHC*H*HO), 3.64 - 3.67 (1H, m, CHCH*H*O), 3.71 (1H, d, *J* = 14.1, NC*H*H), 3.79 (1H, dd, 11.2, 3.2, CHC*H*HO), 5.32 (2H, q, *J* = 11.2, OC*H*$_2$Ar), 5.40 (2H, q, *J* = 11.8, OC*H*$_2$Ar), 7.04 - 7.15 (5H, m, Ar*H*), 7.30 - 7.42 (8H, m, Ar*H*), 7.88 (2H, d, *J* = 7.7, Ar*H*), 7.91 (2H, d, *J* = 8.5, Ar*H*), 8.23 (2H, d, *J* = 8.8, Ar*H*), 8.27 (2H, d, *J* = 8.5, Ar*H*), 8.32 (1H, s, Ar*H*), 8.36 (1H, s, Ar*H*); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 40.0 (CH), 42.9 (CH), 55.5 (CH_2), 65.1 (CH_2), 65.4 (CH_2), 66.8 (CH_2), 73.1 (CH_2), 124.7 (CH), 124.9 (CH), 125.4 (CH), 125.4 (CH), 126.5 (CH), 126.6 (CH), 126.9 (CH), 128.1 (CH), 128.4 (CH), 128.6 (CH), 128.8 (CH), 129.1 (C), 129.3 (CH), 129.4 (CH), 129.6 (C), 131.3 (C), 131.4 (C) 140.5 (C); MS (ES^+) *m/z* 574 [$M+H^+$]; HRMS (ES^+) calcd. For $C_{41}H_{36}NO_2$, 574.2741 [$M+H^+$], found 574.2745.

(2*S*, 3*S*)-1-Ethyl-aziridine-2,3-dicarboxylic acid diethyl ester (46)



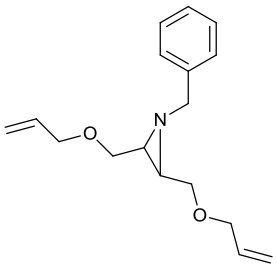
A known compound synthesised using a reported procedure.[67] 60% sodium hydride in mineral oil (1.29 g, 32.2 mmol, 2.1 eq) was washed with dry petrol (2 x 5 mL) then dried *in vacuo*. Ethyl iodide was prepared by passing it through a plug of neutral activated alumina (brockman grade I). A solution of **41** (2.87 g, 15.3 mmol, 1.0 eq) in DMF (14.1 mL) was added to the sodium hydride and stirred at 0 ^{o}C for 15 minutes then the ethyl iodide (4.79 mg, 30.6 mmol, 2.0 eq) added and stirred for 12 h at room temperature. The reaction was quenched with ammonium chloride (20 mL) and extracted with diethyl ether (3 x 40 mL). The combined organics were then washed with water (60 mL), brine (200 mL), dried ($MgSO_4$) and concentrated *in vacuo* leaving a light yellow oil. Purification by flash chromatography (10 – 15% EtOAc in petrol) yielded **46** as a colourless oil (1.36 g, 32%). R_f = 0.33 (15% EtOAc in petrol); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12 (3H, t, *J* = 7.2, NCH_2CH_3), 1.24 – 1.25 (6H, m, CH_3), 2.74 – 2.83 (2H, m, NC*H*H, C*H*), 2.95 – 3.02 (2H, m, NCH*H*, C*H*), 4.22 (4H, m, CO_2CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2 (CH_3), 14.4 (CH_3), 41.0 (CH), 43.7 (CH), 45.8 (CH_2), 61.6 (CH_2), quaternary carbon not observed; MS (ES^+) *m/z* 216 $[M+H]^+$, 238 $[M+Na]^+$.

(2*S*, 3*S*)-1-Ethyl-3-hydroxymethyl-aziridin-2-yl)-methanol (47)



A novel compound synthesised using a modified procedure[180] and work-up.[71] A suspension of $LiAlH_4$ (106 mg, 2.80 mmol, 3.0 eq) in diethyl ether (5 mL) was cooled to 0 ^oC. A solution of **46** (200 mg, 0.90 mmol, 1.0 eq) in diethyl ether (2 mL) was first cooled to 0 ^oC then added dropwise. The mixture was stirred for 2 h at 0 ^oC then allowed to warm to room temperature and stirred for 3 h. The reaction was quenched by the careful dropwise addition of water (0.11 mL) followed by 10% NaOH (0.16 mL) then water (0.26 mL) and stirred vigorously for 20 minutes at 0 ^oC before being filtered. The filter cake was then washed well with warm ether (200 mL) and the filtrate then concentrated *in vacuo* yielding **47** as a white solid requiring no further purification (57 mg, 49%). m.p. 88 – 91 ^oC (powder, Et_2O); ^1H NMR (400 MHz, MeOD) δ 1.22 (3H, t, *J* = 7.2, C*H*$_3$), 1.74 (1H, m, C*H*), 2.13 (1H, dt, *J* = 8.3, 3.7, C*H*), 2.49 (1H, dq, *J* = 12.0, 7.2, NCH*H*), 2.81 (1H, dq, *J* = 12.0, 7.2, NC*H*H), 3.45 (1H, dd, *J* = 11.6, 6.5, CH*H*OH), 3.57 (1H, dd, *J* = 11.6, 5.1, C*H*HOH), 3.76 (1H, dd, *J* = 12.6, 8.3, CH*H*OH), 3.92 (1H, dd, *J* = 12.6, 3.7, C*H*HOH); ^{13}C NMR (100 MHz, MeOD) δ 15.0 (CH_3) 43.4 (CH), 45.1 (CH), 46.4 (CH_2), 58.8 (CH_2), 64.6 (CH_2); MS (ES^+) *m/z* 132 $[M+H]^+$; HRMS (ES^+) calcd. For $C_6H_{14}NO_2$, 132.1016 $[M+H]^+$, found 132.1021.

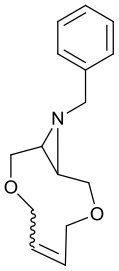
(2*S*, 3*S*)-2,3-*Bis*-allyloxymethyl-1-benzyl-aziridine (50)



A novel compound synthesised using standard alkylation conditions. 60% sodium hydride in mineral oil (37 mg, 0.93 mmol, 2.3 eq) was washed with *n*-pentane (2 x 1 mL) and dried *in vacuo*. DMF (0.5 mL) was added and the suspension cooled to 0 ^{o}C. A solution of **43** (78 mg, 0.40 mmol, 1.0 eq) in DMF (0.5 mL) was cooled to 0 ^{o}C then added dropwise. The mixture was stirred at 0 ^{o}C for 30 minutes before neat allyl bromide (122 mg, 1.01 mmol, 2.5 eq) was added dropwise and the mixture allowed to warm to room temperature and stirred overnight. The reaction was quenched with water (5 mL) and extracted with EtOAc (4 x 2 mL). The combined organic extracts were then washed with water (8 x 2 mL) and brine (2 mL), dried ($MgSO_4$) and concentrated *in vacuo* leaving a yellow oil. Purification by flash chromatography (20% EtOAc in petrol) yielded **50** as a colourless oil (56 mg, 51%). R_f = 0.22 (20% EtOAc in petrol); IR (thin film) 2848, 1646, 1496, 1452, 1351, 1263, 1097, 991, 920, 817, 731, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.79 - 1.85 (1H, m, NC*H*), 2.20 (1H, dt, *J* = 7.6, 3.5, NC*H*), 3.35 (1H, dd, *J* = 10.6, 6.0, CHC*H*HO), 3.40 (1H, dd, *J* = 10.6, 5.2, CHCH*H*O), 3.48 (1H, d, *J* = 13.8, NCH*H*), 3.62 (1H, dd, *J* = 11.3, 7.6, CHC*H*HO), 3.73 (1H, dd, *J* = 11.3, 3.7, CHCH_2O), 3.86 (1H, d, *J* = 13.5, NC*H*H), 3.83 – 3.94 (4H, m, CH_2), 5.08 (2H, dd, *J* = 20.0, 10.4, CH=C*H*H), 5.16 (2H, dd, *J* = 27.6, 17.2, CH=CH*H*), 5.73 – 5.82 (2H, m, C*H*=CHH), 7.15 (1H, t, *J* = 7.2, Ar*H*), 7.23 (2H, t, *J* = 7.3, Ar*H*), 7.32 (2H, d, *J* = 7.3, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.8 (CH), 42.2 (CH), 55.5 (CH_2Ph), 66.2 (CH_2), 71.7 (CH_2), 71.8 (CH_2), 72.2 (CH_2), 116.9 (=CH_2), 117.2 (=CH_2), 126.8 (CH), 128.0

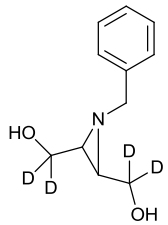
(CH), 128.3 (CH), 134.5 (HC=), 134.7 (HC=), 139.8 (C); MS (ES^+) *m/z* 274 [$M+H^+$]; HRMS (ES^+) calcd. For $C_{17}H_{24}NO_2$, 274.1802 [$M+H^+$], found 274.1809.

(1S, 5E, 10S) and (1S, 5Z, 10S)-11-Benzyl-3,8-dioxa-11-aza-bicyclo[8.1.0]undec-5-ene (51)



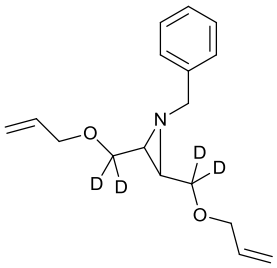
A novel compound synthesised using a modified procedure.[179] Dry DCM (70 mL) was degassed by freeze thaw under vacuum, and a solution of **50** (44 mg, 0.16 mmol, 1.0 eq) in dry dichloromethane (10 mL) was degassed in the same way before it was added *via* cannula to the main solution. Grubbs I catalyst (13 mg, 10 mol%) was added and the violet solution stirred at room temperature overnight. Additional Grubbs I catalyst (11 mg, 8.5 mol%) was added and the solution heated slowly to 50 ^oC. After 5 h the solution was concentrated *in vacuo* leaving a dark brown oil. Purification by flash chromatography (30 – 50% gradient EtOAc in petrol) then further flash chromatography (2% MeOH in dichloromethane) yielded **51** as an off white solid of moderate purity (6 mg, 14%). Full data was not obtained due to decomposition of the sample under NMR conditions. R_f = 0.31 (2% MeOH in dichloromethane); ^1H NMR (400 MHz, $CDCl_3$) δ 1.43 – 1.57 (1H, m, NC*H*), 1.75 – 1.84 (1H, m, NC*H*), 2.94 (1H, dd, *J* = 12.5, 8.4, CH*H*), 3.34 (1H, d, *J* = 13.7, NCH*H*), 3.41 – 3.48 (1H, m, C*H*H), 3.68 (1H, d, *J* = 13.7, NC*H*H), 3.66 – 3.75 (2H, m, CH_2), 4.11 (1H, d, *J* = 12.8, CH*H*), 4.27 – 4.38 (3H, m, CH_2, C*H*H), 5.93 – 6.06 (2H, m, C*H*=), 7.14 – 7.28 (5H, m, Ar*H*); MS (ES^+) *m/z* 246 $[M+H]^+$.

(2*S*, 3*S*)-(1-Benzyl-3-hydroxy($^2H_2$)methyl-aziridin-2-yl)-($^2H_2$)methanol (52)



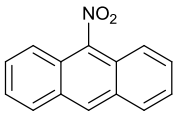
A novel compound synthesised using standard reduction conditions. Lithium aluminium deuteride (606 mg, 14.4 mmol, 8.0 eq) was suspended in THF (14 mL) and cooled to -10 ^oC. A solution of ester **43** (500 mg, 1.81 mmol, 1.0 eq) in THF (3.2 mL) was added dropwise *via* syringe and the mixture stirred at -10 ^oC for 4 h. EtOAc (8 mL) was carefully added followed by 50% EtOAc in water (16 mL). The resulting gel was carefully washed with EtOAc (75 mL) and the filtrate dried ($MgSO_4$) then concentrated *in vacuo*. Purification by flash chromatography (5% MeOH in dichloromethane) gave **52** as a white solid (135 mg, 38%). m.p. 109 – 111 ^oC (powder, 5% MeOH in dichloromethane); R_f = 0.39 (10% MeOH in dichloromethane); IR (thin film) 3267, 3031, 2752, 2581, 2081, 1431, 1354, 1260, 1156, 969, 726, 692 cm^{-1}; ^1H NMR (400 MHz, MeOD) δ 2.02 (1H, d, *J* = 3.6, NC*H*), 2.24 (1H, d, *J* = 3.6, NC*H*), 3.62 (1H, d, *J* = 13.8, NCH*H*), 4.01 (1H, d, *J* = 13.7, NC*H*H), 4.94 (2H, s, O*H*), 7.23 – 7.30 (1H, m, Ar*H*), 7.36 (2H, t, *J* = 7.7, Ar*H*), 7.45 (2H, d, *J* = 7.2, Ar*H*); ^{13}C NMR (100 MHz, MeOD) δ 43.5 (CH), 45.6 (CH), 56.0 (CH_2Ph), 58.5 (CD_2OH), 63.7 (CD_2OH), 128.2 (CH), 129.3 (CH), 129.5 (CH), 140.7 (C); MS (ES^+) *m/z* 198 $[M+H]^+$, 220 $[M+Na]^+$; HRMS (ES^+) calcd. For $C_{11}H_{12}D_4NO_2$, 198.1427 $[M+H]^+$, found 198.1426.

(2*S*, 3*S*)-2,3-*Bis*-allyloxy($^2H_2$)methyl-1-benzyl-aziridine (53)



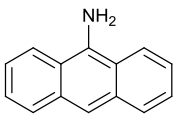
A novel compound synthesised using standard alkylation conditions. 60% sodium hydride in mineral oil (52 mg, 1.30 mmol, 2.3 eq) was washed with *n*-pentane (2 x 1 mL) and dried *in vacuo*. DMF (0.5 mL) and 15-crown-5 (12 mg, 10 mol%) were added and the suspension cooled to 0 ^oC. A solution of **52** (111 mg, 0.56 mmol 1.0 eq) in DMF (0.5 mL) was cooled to 0 ^oC then added dropwise. The mixture was stirred at 0 ^oC for 30 minutes before neat allyl bromide (170 mg, 1.41 mmol, 2.5 eq) was added dropwise and the mixture allowed to warm to room temperature and stirred overnight. The reaction was quenched with water (5 mL) and extracted with EtOAc (4 x 2 mL). The combined organic extracts were then washed with water (8 x 2 mL) and brine (2 mL), dried ($MgSO_4$) then concentrated *in vacuo* leaving a yellowish oil. Purification by flash chromatography (20% EtOAc in petrol) gave **53** as a colourless oil (115 mg, 74%). R_f = 0.32 (20% EtOAc in petrol); IR (thin film) 2848, 1495, 1452, 1357, 1188, 1095, 1046, 921, 730, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.80 (1H, d, *J* = 3.0, NC*H*), 2.18 (1H, d, *J* = 3.0, NC*H*), 3.47 (1H, d, *J* = 13.8, NCH*H*Ph), 3.87 (5H, m, NC*H*HPh, OCH_2), 5.03 – 5.22 (4H, m, CH=CH_2), 5.72 – 5.84 (2H, m, C*H*=CH_2), 7.15 (1H, t, *J* = 7.3, Ar*H*), 7.23 (2H, t, *J* = 7.3, Ar*H*), 7.32 (2H, d, *J* = 7.3, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.6 (CH), 42.1 (CH), 55.5 (CH_2Ph), 65.5 (m, CD_2), 71.5 (m, CD_2), 71.6 (CH_2), 71.7 (CH_2), 116.8 (=CH_2), 117.2 (=CH_2), 126.8 (CH), 128.0 (CH), 128.3 (CH), 134.6 (HC=), 134.8 (HC=), 139.8 (C); MS (ES^+) *m/z* 278 $[M+H]^+$; HRMS (ES^+) calcd. For $C_{17}H_{20}D_4NO_2$, 278.053 $[M+H]^+$, found 278.2057.

9-Nitro-anthracene (140)



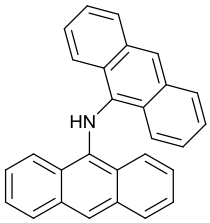
A known compound synthesised using a reported procedure.[80] Anthracene (10.0 g, 56.0 mmol, 1.0 eq) was suspended in glacial acetic acid (40 mL) and the temperature kept below 30 ^{o}C by use of a water bath. Concentrated nitric acid (4 mL) was added dropwise to the vigorously stirred mixture then stirred vigorously for 1 h until homogeneous. Concentrated HCl (50 mL) in glacial acetic acid (50 mL) was added slowly, forming a pale yellow precipitate which was filtered and washed with glacial acetic acid (3 x 24 mL) then water until neutral. The solid was collected and treated with a warm (60 – 70 ^{o}C) solution of 10% NaOH (100 mL), filtered and washed with water until neutral then air dried. The solid was recrystallised from hot glacial acetic acid to yield **140** as yellow needles (8.73 g, 70%). m.p. 146 – 148 ^{o}C (AcOH) (Lit 146 ^{o}C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (2H, tm, *J* = 7.4, Ar*H*), 7.62 (2H, tm, *J* = 7.4, Ar*H*), 7.92 (2H, dd, *J* = 8.8, 0.8, Ar*H*), 8.00 (2H, d, *J* = 8.6, Ar*H*), 8.54 (1H, s, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 121.4 (CH), 122.6 (C), 126.2 (CH), 128.4 (CH), 128.9 (CH), 130.4 (CH), 130.8 (C), 144.3 (C).

Anthracen-9-ylamine (59)



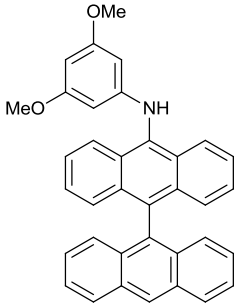
A known compound synthesised using a reported procedure.[80] 9-nitroanthracene **140** (3.16 g, 14.2 mmol, 1.0 eq) was suspended in glacial acetic acid (63 mL) and heated with stirring to 80 ^{o}C for 1.5 h until homogeneous. A slurry of $SnCl_2$ (13.4 g, 70.8 mmol, 5.0 eq) in concentrated HCl (47.5 mL) was added dropwise, the mixture was stirred for 30 minutes at 80 ^{o}C then allowed to cool to room temperature. The light yellow precipitate was filtered off and washed with concentrated HCl (3 x 5 mL). After drying the solid was treated with 5% NaOH solution (75 mL) for 15 minutes with occasional manual stirring. The dark mustard solid was filtered and washed with water until neutral then air dried to give **59** as a dark orange solid (2.09 g, 76%). m.p. 116 ^{o}C (dec.); IR (thin film) 3366, 1620, 1427, 1364, 857, 813, 717, 622 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.86 (2H, br s, N*H*$_2$), 7.38 – 7.47 (4H, m, Ar*H*), 7.89 (1H, s, Ar*H*), 7.93 – 7.98 (4H, m, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 116.3 (CH), 118.3 (C), 121.1 (CH), 123.8 (CH), 125.3 (CH), 129.0 (CH), 132.1 (C), 137.9 (C); MS (ES$^+$) *m/z* 194 $[M+H]^+$, 216 $[M+Na]^+$.

Di-anthracen-9-yl-amine (61)



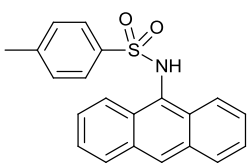
A novel compound synthesised using a modified procedure.[79] 9-aminoanthracene **59** (97 mg, 0.50 mmol, 1.0 eq), 9-bromoanthracene (129 mg, 0.50 mmol, 1.0 eq), sodium *tert*-butoxide (67 mg, 0.70 mmol, 1.4 eq), palladium acetate (3 mg, 2 mol%) and xphos (10 mg, 4 mol%) were placed in a microwave tube flushed with nitrogen. Toluene (1 mL) was added and the tube sealed. Irradiation for 30 minutes (150 ^{o}C, 250 W) resulted in a black suspension which, when concentrated *in vacuo,* yielded a black tar. Purification by column chromatography (15% dichloromethane in petrol + 0.5% triethylamine) resulted in slow degradation allowing a yellow solid to be collected containing minor impurities (60 mg, ~32%). Obtained data is limited due to poor stability. R_f = 0.2 (20% dichloromethane in petrol + 1% triethylamine); ^{1}H NMR (400 MHz, C_6D_6) δ 6.60 (1H, s, N*H*), 6.96 (4H, dd, *J* = 9.0, 6.7, Ar*H*), 7.23 (4H, dd, *J* = 8.4, 6.7, Ar*H*), 7.91 (4H, d, *J* = 8.4, Ar*H*), 8.02 (4H, d, *J* = 9.0, Ar*H*), 8.15 (2H, s, Ar*H*); MS (ES^+) *m/z* 370 $[M+H]^+$, 392 $[M+Na]^+$.

9-(Anthracen-10-yl)-*N*-(3,5-dimethoxyphenyl)anthracen-10-amine (64)



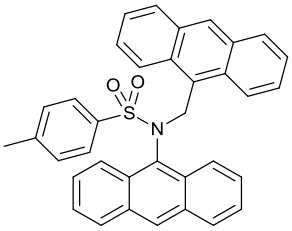
A novel compound synthesised using modified Buchwald amination conditions.[79] *N*-(3,5-dimethoxyphenyl)anthracen-10-amine **63** (50 mg, 0.15 mmol, 1.0 eq), 9-bromoanthracene (40 mg, 0.15 mmol, 1.0 eq), sodium *tert*-butoxide (20 mg, 0.21 mmol, 1.4 eq), palladium acetate (1.2 mg, 2 mol%) and xphos (4 mg, 4 mol%) were placed in a dry microwave tube under nitrogen. Toluene (0.4 mL) was added and the mixture irradiated with microwaves (250 W, 150 ^{o}C) for 30 minutes. The crude mixture was filtered through celite which was washed with dichloromethane (10 mL) and the filtrate concentrated *in vacuo*. Purification by flash chromatography (10% EtOAc in petrol) yielded **64** as a yellow solid (76 mg, 38%). R_f = 0.17 (10% EtOAc in petrol); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.76 (6H, s, C*H*$_3$), 5.95 (2H, d, *J* = 2.2, Ar*H*), 6.01 (1H, t, *J* = 2.2, Ar*H*), 6.16 (1H, br s, N*H*), 7.10 – 7.20 (8H, m, Ar*H*), 7.40 – 7.48 (4H, m, Ar*H*), 8.16 (2H, d, *J* = 8.6, Ar*H*), 8.36 (2H, d, *J* = 8.6, Ar*H*), 8.69 (1H, s, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.2 (CH_3), 90.4 (CH), 93.4 (CH), 124.0 (CH), 125.4 (CH), 125.91 (CH), 125.96 (CH), 126.02 (CH), 126.9 (CH), 127.3 (CH), 127.4 (CH), 128.6 (CH), 129.3 (C), 131.6 (C), 131.7 (C), 132.1 (C), 132.4 (C), 132.8 (C), 150.2 (C), 161.9 (C), 1 x (C) not observed; MS (ES^+) *m/z* 506 $[M+H]^+$, 228 $[M+Na]^+$; HRMS (ES^+) calcd. For $C_{36}H_{27}NNaO_2$ = 528.1934 $[M+Na]^+$ found 528.1936.

_N_-Anthracen-9-yl-4-methyl-benzenesulfonamide (67)



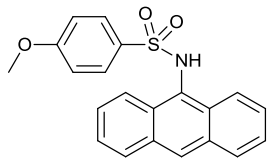
A novel compound synthesised using a modified procedure.[181] 9-aminoanthracene **59** (200 mg, 1.04 mmol, 1.0 eq), *p*-toluenesulfonyl chloride (197 mg, 1.04 mmol, 1.0 eq) and DMAP (20 mg, 0.17 mmol, 0.16 eq) were placed in a round bottom flask and pyridine added (5 mL). The mixture was stirred at room temperature overnight. The reaction mixture was quenched with 2N HCl (2 mL) and extracted with dichloromethane (3 x 5ml), dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow solid which was recrystallised (ethanol) to give **67** as cream crystals (211 mg, 58%). m.p. 244 – 246 ^oC (ethanol); IR (thin film) 3274, 2970, 1380, 1330, 1157 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.37 (3H, s, C*H*$_3$), 6.72 (1H, s, N*H*), 7.11 (2H, d, *J* = 8.2, Ar*H*), 7.33 (2H, dd, *J* = 7.6, 8.4 Ar*H*), 7.42 (2H, dd, 7.6, 8.2 Ar*H*), 7.49 (2H, d, *J* = 8.2, Ar*H*), 7.95 – 8.03 (4H, m, Ar*H*), 8.45 (1H, s, Ar*H*); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 21.6 (CH_3), 124.1 (CH), 125.8 (CH), 126.6 (CH), 127.7 (C), 128.4 (CH), 128.7 (CH), 130.0 (CH), 130.6 (CH), 132.2 (C), 134.5 (C), 137.2 (C), 144.5 (C); MS (ES^+) *m/z* 348 $[M+H]^+$, 370 $[M+Na]^+$, 386 $[M+K]^+$; HRMS (ES^+) calcd. For $C_{21}H_{17}NNaO_2S$ 370.0872 $[M+Na]^+$ found 370.0873.

_N_-Anthracen-9-yl-N-anthracen-9-ylmethyl-4-methyl-benzenesulfonamide (68)



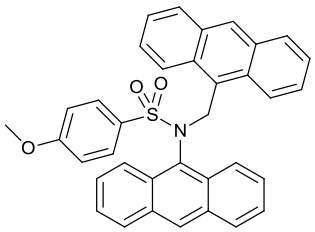
A novel compound synthesised using a modified procedure.[182] Acetone was dried by standing over activated 4 Å molecular sieves overnight. To a flask containing *N*-tosyl amino anthracene **67** (400 mg, 1.20 mmol, 1.0 eq), 9-bromoanthracene (890 mg, 3.50 mmol, 3.0 eq), potassium carbonate (479 mg, 3.50 mmol, 3.0 eq) and potassium iodide (191 mg, 1.20 mmol, 1.0 eq) was added the dried acetone (22 mL) and the mixture heated to reflux for 3 days. The reaction mixture was filtered through celite which was washed with dichloromethane (200 mL). The filtrate was concentrated *in vacuo* and purified by flash chromatography (50% dichloromethane in petrol) followed by trituration (diethyl ether) to give **68** as a light yellow powder (497 g, 77%). m.p. 242 – 244 ^{o}C (powder, Et_2O); UV (dichloromethane) λ_{max}, nm: 353, 372, 394; IR (thin film) 2970, 1349, 1158, 731, 662 cm^{-1}; ^{1}H NMR (700 MHz, $CDCl_3$) δ 2.48 (3H, s, C*H*$_3$), 6.23 (2H, s, C*H*$_2$), 6.88 (2H, dd, *J* = 7.7, 8.5 Ar*H*), 6.96 (2H, dd, *J* = 7.7, 8.4 Ar*H*), 7.13 – 7.19 (4H, m, Ar*H*), 7.27 (2H, dd, *J* = 8.2, 7.5 Ar*H*), 7.51 (2H, dd, *J* = 8.9, 7.5 Ar*H*), 7.64 (2H, d, *J* = 8.4, Ar*H*), 7.66 (2H, d, *J* = 8.5, Ar*H*), 7.79 (2H, d, *J* = 8.2, Ar*H*), 7.91 (2H, d, *J* = 8.9, Ar*H*), 8.03 (1H, s, Ar*H*), 8.08 (1H, s, Ar*H*); ^{13}C NMR (176 MHz, $CDCl_3$) δ 21.6 (CH_3), 46.3 (CH_2), 123.8 (CH), 124.1 (CH), 124.3 (CH), 124.6 (CH), 125.3 (CH), 125.5 (CH), 125.8 (C), 128.1 (CH), 128.2 (CH), 128.4 (CH), 128.5 (CH), 129.6 (CH), 129.7 (C), 130.6 (C), 131.36 (C), 131.42 (C), 131.9 (C), 137.6 (C), 143.6 (C), 1 x (CH, Ar) not observed; MS (ES$^+$) *m/z* 560 [M+Na]$^+$; HRMS (ES$^+$) calcd. For $C_{36}H_{27}NNaO_2S$ = 560.1655 [M+Na]$^+$, found 560.1653.

_N_-Anthracen-9-yl-4-methoxy-benzenesulfonamide (69)



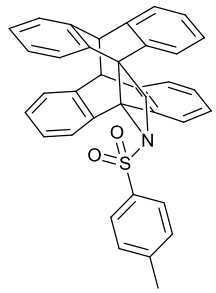
A novel compound synthesised using a modified procedure.[181] 9-aminoanthracene **59** (500 mg, 2.60 mmol, 1.0 eq), 4-methoxybenzenesulfonyl chloride (537 mg, 2.60 mmol, 1.0 eq) and DMAP (50 mg, 0.42 mmol, 0.16 eq) were placed in a round bottom flask and pyridine added (12.5 mL). The mixture was stirred at room temperature overnight, then quenched with 2N HCl (50 mL) and extracted with dichloromethane (3 x 15ml). The combined organics were washed with 5% HCl (4 x 15 mL) then dried ($MgSO_4$) and concentrated *in vacuo* leaving a yellow solid, which was recrystallised twice (ethanol) to give **69** as pale cream crystals (429 mg, 45%). m.p. 208 – 210 ^oC (ethanol); IR (thin film) 3265, 1594, 1577, 1496, 1383, 1329, 1302, 1262, 1151, 828, 730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.79 (3H, s, C*H*$_3$), 6.76 (2H, d, *J* = 9.0, Ar*H*), 6.82 (1H, s, N*H*), 7.34 (2H, dd, *J* = 8.9, 7.6, Ar*H*), 7.42 (2H, dd, *J* = 8.4, 7.6, Ar*H*), 7.51 (2H, d, *J* = 9.0, Ar*H*), 7.96 (2H, d, *J* = 8.4, Ar*H*), 8.00 (2H, d, *J* = 8.9, Ar*H*), 8.43 (1H, s, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.6 (CH_3), 114.1 (CH), 123.7 (CH), 125.4 (CH), 126.3 (CH), 128.0 (CH), 128.4 (CH), 129.6 (CH), 130.2 (C), 131.3 (C), 131.8 (C), 147.7 (C), 163.2 (C); MS (ES^+) *m/z* 386 $[M+Na]^+$; HRMS (ES^+) calcd. For $C_{21}H_{17}NNaO_3S$ = 386.0821 $[M+Na]^+$, found 386.0824.

_N_-Anthracen-9-yl-N-anthracen-9-ylmethyl-4-methoxy-benzenesulfonamide (70)



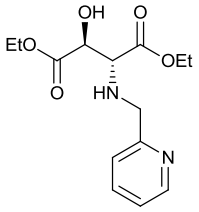
A novel compound synthesised using a modified procedure.[182] **69** (150 mg, 0.41 mmol, 1.0 eq), 9-bromomethylanthracene (106 mg, 0.41 mmol, 1.0 eq), potassium iodide (7 mg, 0.041 mmol, 0.1 eq) and potassium carbonate (86 mg, 0.62 mmol, 1.5 eq) were placed in a microwave tube and flushed with nitrogen gas. Acetonitrile (6 mL) was added and the mixture irradiated with microwaves (300W, 110 ^{o}C) for 15 minutes. The crude mixture was then filtered through celite, which was washed with dichloromethane and the filtrate concentrated *in vacuo*. Purification by flash chromatography (40% dichloromethane in petrol) followed by trituration in diethyl ether yielded **70** as a light yellow powder (105 mg, 48%). m.p. 236 – 239 ^{o}C (powder, Et_2O); R_f 0.26 (40% dichloromethane in petrol); IR (thin film) 1595, 1494, 1444, 1323, 1257, 1150, 1089, 731 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.89 (3H, s, C*H*$_3$), 6.24 (2H, s, C*H*$_2$), 6.88 – 6.99 (6H, m, Ar*H*), 7.13 – 7.19 (4H, m, Ar*H*), 7.53 (2H, d, *J* = 8.9, Ar*H*), 7.65 (4H, m, Ar*H*), 7.81 (2H, d, *J* = 8.8, Ar*H*), 7.92 (2H, d, *J* = 9.0, Ar*H*), 8.03 (1H, s, Ar*H*), 8.08 (1H, s, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 46.3 (CH_2), 55.8 (CH_3), 114.2 (CH), 123.8 (CH), 124.1 (CH), 124.4 (CH), 124.7 (CH), 125.4 (CH), 125.6 (CH), 126.0 (C), 128.1 (CH), 128.4 (CH), 128.5 (CH), 129.7 (C), 130.3 (CH), 130.7 (C), 131.4 (C), 131.5 (C), 131.9 (C) 132.4 (C) 1 x (CH, Ar), 1x (C, Ar) not observed; MS (ES$^+$) *m/z* 576 [M+Na]$^+$; HRMS (ES$^+$) calcd. For $C_{36}H_{27}NNaO_3S$ = 576.1604 [M+Na]$^+$, found 576.1608.

3a,8[1',2']:9,13b[1'',2'']-Dibenzeno-1*H*-dibenzo[3,4:7,8]cycloocta[1,2]azetidine (*N*-4-methyl-benzenesulfonamide), 2,3,8,9-tetrahydro- (9CI) (71)



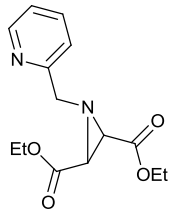
A novel compound synthesised using standard photochemical conditions. **68** (20 mg, 0.037 mmol) was placed in a schlenk tube and made up with anhydrous dichloromethane (50 mL). It was then subjected to at least three cycles of freeze, pump (~ 1 mB) thaw and bubbling through argon. The schlenk was then placed under an argon atmosphere and irradiated with a 125 W medium pressure Hg lamp through a window of multi coated glass filter (Edmund Optics 365 nm band pass ± 10 nm, P/N NT65-191) for 2 h then concentrated *in vacuo.* Purification by column chromatography (50% dichloromethane in petrol) yielded **71** as a colourless solid (8.7 mg, 44%). m.p. 200 ^{o}C (dec.); R_f = 0.33 (50% dichloromethane in petrol); ^{1}H NMR (600 MHz, CD_2Cl_2) δ 2.56 (3H, s, C*H*$_3$), 4.53 (1H, d, *J* = 11.6, C*H*), 4.61 (1H, d, *J* = 11.6, C*H*), 4.91 (2H, s, C*H*$_2$), 6.84 – 6.97 (10H, m, Ar*H*), 7.00 – 7.04 (4H, m, ArH), 7.37 – 7.41 (2H, m, Ar*H*), 7.54 (2H, d, *J* = 8.0, Ar*H*), 8.00 (2H, d, *J* = 8.2, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6 (CH_3), 46.8 (CH_2), 52.5, (CH) 53.9 (CH) 123.3 (CH), 124.7 (CH), 125.7 (CH), 125.8 (CH), 126.3 (CH), 126.6 (CH), 126.9 (CH), 128.1 (CH), 130.0 (CH), quaternary carbons not observed; MS (ES^+) *m/z* 538.1 $[M+H]^+$, 560 $[M+Na]^+$; HRMS (ES^+) Calc. For $C_{36}H_{28}NO_2S$ = 538.1835 $[M+H]^+$, found = 538.1839.

(2*S,3*R**)-2-Hydroxy-3-[(pyridin-2-ylmethyl)-amino]-succinic acid diethyl ester (74)**



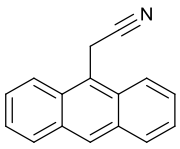
A known compound synthesised following a reported procedure.[47] (2S*, 3S*)-oxirane-2,3- dicarboxylic acid diethyl ester (3.00 g, 16.0 mmol, 1.0 eq) and 2-picolylamine (2.10 g, 19.2 mmol, 1.2 eq) were dissolved in ethanol (25 mL). The solution was heated to reflux for 12 h. The reaction was allowed to cool to room temperature and solvent removed *in vacuo*. Purification by column chromatography (3% methanol in dichloromethane) yielded **74** as a yellow oil (4.67 g, 99%). R_f = 0.19 (3% methanol in dichloromethane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (6H, t, *J* = 7.2, C*H*$_3$), 3.74 (1H, d, *J* = 3.3, C*H*), 3.88 (1H, d, *J* = 14.9, CH*H*), 4.10 – 4.21 (5H, m, C*H*$_2$, C*H*H), 4.55 (1H, d, *J* = 3.3, C*H*), 7.14 (1H, dd, *J* = 7.5, 5.0, Ar*H*), 7.28 (1H, d, *J* = 7.7, Ar*H*), 7.62 (1H, td, *J* = 7.7, 1.8, Ar*H*), 8.51 (1H, d, *J* = 5.0, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0 (CH_3), 14.1 (CH_3), 52.0 (CH_2), 61.4 (CH_2), 61.6 (CH_2), 64.2 (CH), 72.2 (CH), 122.0 (CH), 122.4 (CH), 136.7 (CH), 149.0 (CH), 159.2 (C), 171.0 (C=O), 172.0 (C=O); MS (ES$^+$) *m/z* 319 [M+Na$^+$].

(2*R,3*R**)-1-Pyridin-2-ylmethyl-aziridine-2,3-dicarboxylic acid bismethylamide (75)**



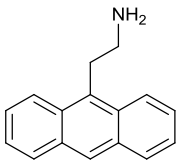
A known compound synthesised using a reported procedure.[47] To a stirred solution of amino alcohol **74** (1.38 g, 4.66 mmol, 1.0 eq) and PPh_3 (1.59 g, 6.06 mmol, 1.3 eq) in THF (13 mL) at 0 °C, was slowly added diethyl azodicarboxylate (1.06 g, 6.06 mmol, 1.3 eq). The reaction was allowed to warm to room temperature and stirred for a further 12 h, then concentrated *in vacuo*. The solid/oil was first triturated with diethyl ether and the excess phosphine and phosphine oxide removed by filtration though celite. The filtrate was concentrated *in vacuo*. Purification by column chromatography (40 – 50% EtOAc in petrol) gave **75** as a yellow oil (251 mg, 19%). R_f = 0.31 (50% EtOAc in petrol); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 – 1.29 (6H, m, C*H*$_3$), 3.03 (1H, br s, NC*H*), 3.16 (1H, br s, NC*H*), 4.10 – 4.32 (6H, m, C*H*$_2$CH$_3$, NC*H*$_2$), 7.15 (1H, t, *J* = 6.0, Ar*H*), 7.44 (1H, d, *J* = 7.8, Ar*H*), 7.65 (1H, td, *J* = 7.8, 1.8, Ar*H*), 8.49 – 8.54 (1H, m, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1 (CH_3), 14.4 (CH_3), 41.1 (CH), 43.9 (CH), 56.2 (CH_2), 61.7 (CH_2), 62.2 (CH_2), 121.9 (CH), 122.1 (CH), 136.6 (CH), 149.2 (CH), 158.0 (C), 166.5(C=O), 170.7 (C=O); MS (ES^+) *m/z* 271 $[M+Na]^+$.

9-Anthryacetonitrile (77)



A known compound synthesised following a reported procedure.[83] A solution of 9-(chloromethyl)anthracene (3.00 g, 13.2 mmol, 1.0 eq) in DMF (43 mL) was added dropwise to a solution of sodium cyanide (1.29 g, 26.4 mmol, 2.0 eq) in DMF (58 mL) at 140 ^{o}C. The mixture was stirred for 4 h then allowed to cool to room temperature. Ice/water (100 mL) was then added and the yellow precipitate collected by filtration. The solid was recrystallised in multiple batches from hot ethanol yielding **77** as bright yellow needles (2.03 g, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.55 (2H, s, C*H*$_2$), 7.52 (2H, ddd, *J* = 8.5, 6.5, 0.8, Ar*H*), 7.62 (2H, ddd, *J* = 8.9, 6.5, 1.3, Ar*H*), 8.04 (2H, d, *J* = 8.5, Ar*H*), 8.14 (2H, d, *J* = 8.9, Ar*H*), 8.44 (1H, s, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.3 (CH_2), 117.8 (C), 120.9 (C), 123.0 (CH), 125.4 (CH), 127.3 (CH), 128.9 (CH), 129.5 (CH), 129.9 (C), 131.5 (C); MS (ES^+) *m/z* 240 $[M+Na]^+$;

2-Anthracen-9-yl-ethylamine (78)



A known compound prepared initially by reported procedure **Method A**[83] and later using novel synthesis **Method B**.

Method A: A solution of 9-anthrylacetonitrile **77** (2.42 g, 11.1 mmol, 1.0 eq) in THF (40 mL) was added dropwise *via* cannula to a suspension of lithium aluminium hydride (1.14 g, 30.1 mmol, 2.7 eq) in THF (79 mL). The mixture was then heated to reflux for 4 h. After cooling to room temperature a 50:50 mixture of methanol and water (10 mL) was added dropwise. The resulting aluminium solid was removed by filtration and the filtrate concentrated *in vacuo*. The solid was

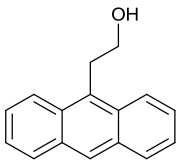
purified by column chromatography (5% sat. $NH_4OH_{(aq)}$ in methanol), to give **78** as a yellow solid (660 mg, 27%).

Method B: 10% Palladium on carbon (2 mg) was added to a solution of azide **83** (1.10 g, 4.45 mmol, 1.0 eq in THF (31 mL). The flask was vacuum filled with hydrogen, and stirred overnight under a slight positive pressure of hydrogen. The resulting mixture was filtered through celite and the plug washed with dichloromethane. The filtrate was then concentrated *in vacuo* to give **78** as a yellow solid used without further purification (976 mg, quant.). R_f = 0.43 (5% sat. $NH_4OH_{(aq)}$ in methanol); IR (thin film) 3379, 2919, 1668, 1599, 1317, 1035, 932, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.20 (2H, t, *J* = 7.3, C*H*$_2$), 3.80 (2H, t, *J* = 7.3, C*H*$_2$), 7.43 – 7.55 (4H, m, Ar*H*), 8.01 (2H, d, *J* = 8.4, Ar*H*), 8.32 (2H, d, *J* = 8.8, Ar*H*), 8.36 (1H, s, Ar*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.0 (CH_2), 42.5 (CH_2), 124.4 (CH), 124.9 (CH), 125.7 (CH), 126.1 (CH), 129.3 (CH), 130.1 (C), 131.6 (C), 132.0 (C); MS (ES^+) *m/z* 222 $[M+H]^+$, 443 $[2M+H]^+$.

Oxirane (80)

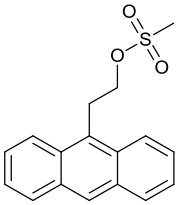
A known compound synthesised using a reported procedure.[84] 2-chloro ethanol (4 g, 40 mmol) was dissolved in water (60 mL). The solution was then frozen using liquid nitrogen. Potassium hydroxide pellets (56 g, 1 mol) were added and the mixture slowly allowed to thaw. The gas which evolved vigorously was directed through a column of $CaCl_2$ then condensed on a cold finger and collected in a flask cooled in an acetone / dry ice bath. ^1H NMR (400 MHz, $CDCl_3$) δ 2.49 (4H, s, C*H*$_2$).

2-Anthracen-9-yl-ethanol (81)



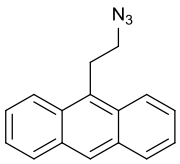
A known compound synthesised using a modified procedure.[84] 9-bromoanthracene (4.10 g, 16.0 mmol, 1.0 eq) was dissolved in anhydrous diethyl ether (100 mL) and cooled to -78 ^{o}C. *n*-Butyl lithium 1.6 M in hexanes (12.0 mL, 19.2 mmol, 1.2 eq) was added dropwise *via* syringe. The green solution was allowed to warm to 0 ^{o}C, then connected directly to a chilled sealed flask containing excess freshly prepared oxirane. The oxirane flask was allowed to warm slowly so that oxirane was slowly bubbled through the solution of lithiated 9-bromoanthracene. Once the supply of oxirane was exhausted the solution was stirred for a further 1 h. Methanol (5 mL) was added dropwise and the solution allowed to warm to room temperature. Saturated ammonium chloride solution (25 mL) was added and the organics separated. The aqueous was extracted with dichloromethane (3 x 15 mL). The combined organics were washed with water (40 mL), brine (40 mL) then dried ($MgSO_4$) and concentrated *in vacuo*. Two recrystallisations from toluene yielded **81** as long yellow/green crystals (1.74 g, 50%). R_f = 0.46 (30% EtOAc in petrol); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (1H, t, *J* = 5.8, O*H*), 3.95 (2H, t, *J* = 7.3, CH_2), 4.10 (2H, m, CH_2), 7.50 (4H, m, Ar*H*), 8.02 (2H, d, *J* = 8.3, Ar*H*), 8.33 (2H, d, *J* = 8.7, Ar*H*), 8.39 (1H, s, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.2 (CH_2), 43.5 (CH_2) 63.6 (CH_2), 124.4 (CH), 125.1 (CH), 126.0 (CH), 126.6 (CH), 129.4 (CH), 130.3 (C), 130.5 (C), 131.7 (C); MS (ES^+) *m/z* 223 $[M+H]^+$, 245 $[M+Na]^+$.

Methanesulfonic acid 2-anthracen-9-yl-ethyl ester (82)



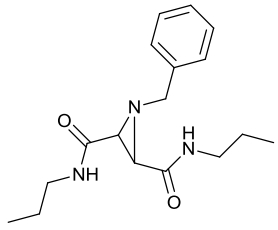
A novel compound synthesised using standard mesylation conditions. 9-Anthryl ethanol (1.70 g, 7.65 mmol, 1.0 eq) was dissolved in dichloromethane (111 mL) and triethylamine (1.54 g, 15.3 mmol, 2.0 eq) was added. The solution was cooled to 0 ^{o}C and mesyl chloride (1.75 g, 13.3 mmol, 2.0 eq) added dropwise by syringe. The solution was stirred for 2 h then quenched with water (50 mL) and the organics separated. The aqueous layer was extracted with dichloromethane (3 x 20 mL) and the combined organics washed with water (20 mL), brine (20 mL) and dried ($MgSO_4$) then concentrated *in vacuo*. Purification by recrystallisation (hot ethanol) yielded **82** as yellow crystals (1.97 g, 86%) which was used immediately following purification. R_f = 0.23 (30% dichloromethane in petrol); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.80 (3H, s, C*H*$_3$), 4.13 (2H, t, *J* = 8.1, C*H*$_2$), 4.58 (2H, t, *J* = 8.1, C*H*$_2$), 7.49 (2H, m, Ar*H*), 7.58 (2H, ddd, *J* = 9.0, 6.7, 1.3, Ar*H*), 8.03 (2H, d, *J* = 8.5, Ar*H*), 8.27 (2H, d, *J* = 9.0, Ar*H*), 8.42 (1H, s, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.0 (CH_2), 37.5 (CH_3), 69.1 (CH_2), 123.7 (CH), 125.1 (CH), 126.5 (CH), 127.2 (C), 127.4 (CH), 129.4 (CH), 130.3 (C), 131.5 (C); MS (ES^+) *m/z* 323 $[M+Na]^+$; HRMS (ES^+) Calc. For $C_{17}H_{16}NNaO_3S$ = 323.0712 $[M+Na]^+$, Found = 323.0712.

9-(2-Azido-ethyl)-anthracene (83)



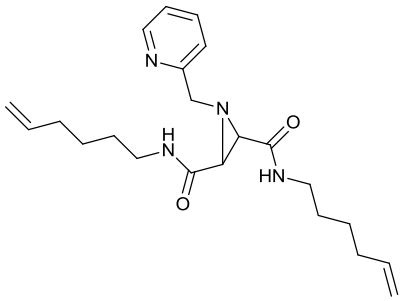
A novel compound synthesised using standard substitution conditions. Mesylate **82** (1.46 g, 4.86 mmol, 1.0 eq) was dissolved in DMF (7.3 mL) and sodium azide (474 mg, 7.29 mmol, 1.5 eq) added. The mixture was heated to 85 ^{o}C and stirred overnight. The solution was cooled to room temperature, then diluted with water (20 mL) and extracted with EtOAc (4 x 15 mL). The combined organics were washed with water (6 x 15 mL), brine (15 mL) then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (10% dichloromethane in petrol) yielded **83** as a yellow solid (1.11 g, 93%) which was used immediately following purification. R_f = 0.29 (10% dichloromethane in petrol); IR (thin film) 2976, 2077, 1623, 1425, 1232, 878, 839, 731 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.68 (2H, t, *J* = 7.6, C*H*$_2$), 3.95 (2H, t, *J* = 7.6, C*H*$_2$), 7.49 (2H, m, Ar*H*), 7.56 (2H, m, Ar*H*), 8.03 (2H, d, *J* = 8.4, Ar*H*), 8.25 (2H, d, *J* = 8.9, Ar*H*), 8.41 (1H, s, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.8 (CH_2), 52.2 (CH_2), 124.7 (CH), 124.9 (CH), 125.8 (CH), 126.8 (CH), 129.4 (CH), 130.0 (C), 130.4 (C), 132.1 (C); MS (ES$^+$) *m/z* 248 $[M+H]^+$, 270 $[M+Na]^+$; HRMS (ES$^+$) Calc. For $C_{16}H_{13}N_3Na$ = 270.1109 $[M+Na]^+$, Found = 270.1112.

(2*S*, 3*S*)-1-Benzyl-aziridine-2,3-dicarboxylic acid bis-propylamide (85)



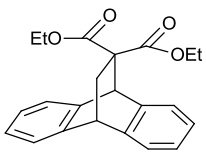
A novel compound synthesised using a modified procedure.[47] (2*S*, 3*S*)-1-Benzyl-aziridine-2,3-dicarboxylic acid diethyl ester **42** (50 mg, 0.18 mmol, 1.0 eq) was dissolved in chloroform (1 mL) and *n*-propylamine (426 mg, 7.20 mmol, 40 eq) added and the solution stirred at room temperature for 4 days. The solution was concentrated *in vacuo* then purified by column chromatography (40 – 50% EtOAc in petrol), yielding **85** as a white solid (38 mg, 70%). m.p. 96 - 98 ^{o}C (powder, EtOAc / petrol); R_f = 0.19 (50% EtOAc in petrol); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.75 (3H, t, *J* = 7.3, C*H*$_3$), 0.81 (3H, t, *J* = 7.3, C*H*$_3$), 1.25 – 1.44 (4H, m, C*H*$_2$), 2.48 (1H, d, *J* = 2.4, NC*H*), 2.91 (1H, d, *J* = 2.4, NC*H*), 2.92 – 3.22 (4H, m, C*H*$_2$), 3.93 (1H, d, *J* = 13.3, NC*H*H), 3.97 (1H, d, *J* = 13.3, NCH*H*), 6.51 – 6.60 (1H, m, N*H*), 6.85 – 6.94 (1H, m, N*H*), 7.21 (5H, m, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.2 (CH_3), 11.4 (CH_3), 22.6 (CH_2), 22.7 (CH_2), 40.6 (CH_2), 41.8 (CH_2), 43.4 (CH), 43.8 (CH), 53.5 (CH_2), 127.3 (CH), 128.40 (CH), 128.43 (CH), 138.8 (C), 165.2 (C=O), 169.3 (C=O); MS (ES^+) *m/z* 326 $[M+Na]^+$; HRMS (ES^+) Calc. For $C_{17}H_{25}N_3NaO_2$ = 326.1839 $[M+Na]^+$, Found = 326.1841.

(2*R,3*R**)-1-Pyridin-2-ylmethyl-aziridine-2,3-dicarboxylic acid bis-hex-5-enylamide (183)**



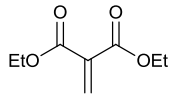
A novel compound synthesised using a modified procedure.[47] **42** (50 mg, 0.18 mmol, 1.0 eq) was dissolved in chloroform (1 mL) and Hex-5-enylamine (356 mg, 3.60 mmol, 20 eq) was added *via* syringe. The solution was warmed to 50 ^{o}C and stirred for 5 days. After cooling to room temperature the solution was concentrated *in vacuo*. Purification by column chromatography (50 – 80% EtOAc in petrol) yielded **182** as a waxy white solid (52 mg, 76%). m.p 56-58 ^{o}C (powder, EtoAc / petrol); R_f = 0.34 (80% EtOAc in petrol); IR (thin film) 3279, 2926, 2857, 1638, 1553, 1434, 1251, 908, 692 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 – 1.41 (4H, m, C*H*$_2$), 1.41 – 1.53 (4H, m, C*H*$_2$), 2.03 (4H, m, C*H*$_2$), 2.71 (1H, br s, NC*H*), 2.98 (1H, br s, NC*H*), 3.01 – 3.27 (4H, m, C*H*$_2$), 4.14 (1H, d, *J* = 14.6, NC*H*H), 4.24 (1H, d, *J* = 14.6, NCH*H*), 4.94 (2H, dm, *J* = 10.2, C*H*H), 4.98 (2H, ddt, *J* = 17.1, 3.5, 1.7, CH*H*), 5.75 (2H, ddt, *J* = 17.1,10.2, 6.7, =C*H*), 6.73 (1H, br s, N*H*), 7.05 – 7.25 (3H, m, Ar*H*, N*H*), 7.63 (1H, td, *J* = 7.7, 1.9, Ar*H*), 8.58 (1H, d, *J* = 4.8, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.1 (CH_2), 28.9 (CH_2), 30.5 (CH_2), 33.3 (CH_2), 77.3 (CH), 114.9 (CH_2), 122.3 (CH), 122.8 (CH), 136.6 (CH), 138.3 (CH), 149.3 (CH), 158.4 (C); MS (ES$^+$) *m/z* 385 $[M+H]^+$, 407 $[M+Na]^+$, 791 $[2M+Na]^+$; HRMS (ES$^+$) Calc. For $C_{22}H_{33}N_4NaO_2$ = 385.2598 $[M+H]^+$, Found = 385.2599.

9,10-Ethanoanthracene-11,11-dicarboxylic acid, 9,10-dihydro-, 11,11-diethyl ester (97)



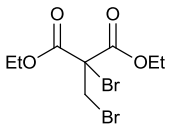
A known compound synthesised using a reported procedure.[102] A round bottom flask was charged with diethyl malonate (5.00 g, 31.2 mmol, 1.0 eq), paraformaldehyde (1.90 g, 62.4 mmol, 2.0 eq), anthracene (5.56, 31.2 mmol, 1.0 eq), copper (II) acetate (1.13 g, 6.2 mmol, 0.2 eq), acetic acid (6.75 mL), and xylene (6.75 mL). The reaction mixture was heated to 100 ^{o}C for 2 h. The temperature was then raised to remove the majority of the acetic acid by distillation. Once most of the acetic acid had been removed, the copper catalyst precipitated. On cooling to room temperature, the precipitated catalyst and unreacted anthracene was removed by filtration, and the filtrate was concentrated *in vacuo*. The resulting oil crystallised on standing overnight and was then recrystallised (ethanol), yielding **97** as colourless crystals containing a minor impurity (7%) of anthracene (5.59 g, 51%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (6H, t, *J* = 7.1, C*H*$_3$), 2.41 (2H, d, *J* = 2.7, C*H*$_3$), 3.88 – 4.02 (4H, m, C*H*$_2$CH$_3$), 4.26 (1H, t, *J* = 2.7, C*H*), 4.90 (1H, s, C*H*), 6.97 – 7.05 (4H, m, Ar*H*), 7.16 – 7.23 (2H, m, Ar*H*), 7.22 – 7.29 (2H, m, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1 (CH_3), 36.5 (CH_2), 44.0 (CH), 49.7 (CH), 59.8 (C), 61.7 (CH_2), 123.3 (CH), 125.7 (CH), 125.8 (CH), 128.5 (CH), 139.9 (C), 144.1 (C), 170.3 (C=O); MS (ES$^+$) *m/z* 351 $[M+H]^+$.

Methylidenemalonic acid diethylester (98)



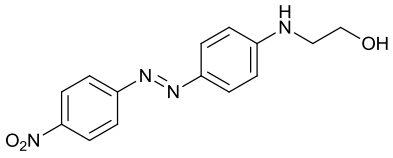
A known compound synthesised using a reported procedure.[102] An aliquot of paraffin oil for oil baths (Fisher Scientific) was distilled under nitrogen up to 250 ^{o}C. After cooling this high boiling point oil was used as the reaction solvent. Anthracene adduct **97** (5.50 g, 15.7 mmol, 1.0 eq) and powdered maleic anhydride were placed in a round bottom flask which had been previously washed with concentrated HCl then oven dried. The high boiling oil (25 mL) was added and the mixture stirred and heated to 225 ^{o}C using an aluminium heating block for 45 minutes. On cooling the maleic anhydride anthracene adduct precipitated and was removed by filtration. The remaining oil was distilled under reduced pressure (72 ^{o}C, 1 mbar) to yield the methylidenemalonic acid diethylester **98** as a colourless oil (1.88 g, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (6H, t, *J* = 7.1, C*H*$_3$), 4.26 (4H, q, *J* = 7.1, C*H*$_2$), 6.48 (2H, s, =C*H*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1 (CH_3), 61.5 (CH_2), 135.1 (C), 136.5 (CH_2), 164.1 (C=O); MS (ES^+) *m/z* 195 $[M+Na]^+$.

2-Bromo-2-bromomethyl-malonic acid diethyl ester (100)



A known compound synthesised using a modified procedure.[103] Carbon tetrachloride was dried over 4 Å molecular sieves overnight. Methylidenemalonic acid diethylester **99** (100 mg, 0.58 mmol, 1.0 eq) was dissolved in the dried carbon tetrachloride (3 mL), and a separate solution of bromine (418 mg, 2.60 mmol, 4.5 eq) in carbon tetrachloride (1 mL) was prepared then added dropwise. The solution was stirred for 2 days at room temperature then concentrated *in vacuo*. Purification by column chromatography (2 - 5% EtOAc in petrol) yielded **100** as a light brown solid (108 mg, 56%). R_f = 0.24 (5% EtOAc in petrol); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (6H, t, *J* = 7.1, C*H*$_3$), 4.05 (2H, s, C*H*$_2$Br), 4.32 (4H, q, *J* = 7.1, C*H*$_2$CH$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9 (CH_3), 35.8 (CH_2), 60.6 (C), 63.7 (CH_2), 64.9 (C=O); MS (ES^+) *m/z* 353 $[2^{79}BrM+Na]^+$, 354 $[^{79}Br^{81}BrM+Na]^+$, 355 $[2^{81}BrM+Na]^+$.

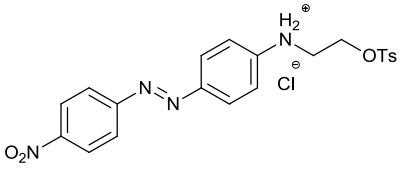
2-[4-(4-Nitro-phenylazo)-phenylamino]-ethanol (103)



A previously reported compound synthesised using a modified procedure.[96] 4-Nitroaniline (4.40 g, 31.9 mmol, 1.0 eq) was finely ground and dissolved in concentrated hydrochloric acid (32 mL) and water (240 mL) by vigorous stirring at room temperature for 3 h. The solution was then cooled to 0 ^{o}C and $NaNO_2$ (2.32 g, 33.6 mmol, 1.1 eq) added portion wise. The mixture was stirred at 0 ^{o}C for 1 h then used immediately in the azo coupling reaction. β-hydroxyethyl aniline (5.00 g, 28.8 mmol, 0.9 eq) was dissolved in acetone (320 mL) and cooled to 0 ^{o}C. To this was

added the diazo solution slowly over 20 minutes *via* dropping funnel kept below 10 ^{o}C with ice. After addition, the red suspension was stirred for a further 1 h before acetic acid (1 mL) was added. 10% sodium hydroxide was added dropwise until the pH reached 3 - 4. The solid red precipitate was filtered and washed with warm and cold water, then dried in a desccicator. To give **103** as a dark orange solid which was used without further purification (7.97 g, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.44 (2H, q, *J* = 4.9, C*H*$_2$), 3.93 (2H, q, *J* = 4.9, C*H*$_2$), 4.73 (1H, s, N*H*), 6.72 (2H, d, *J* = 9.0, Ar*H*), 7.89 (2H, d, *J* = 9.0, Ar*H*), 7.93 (2H, d, *J* = 9.0, Ar*H*), 8.33 (2H, d, *J* = 9.0, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 45.4 (CH_2), 61.1 (CH_2), 112.5 (CH), 122.7 (CH), 124.7 (CH), 126.3 (CH), 145.0 (C), 147.6 (C), 152.1 (C), 156.6 (C); MS (ES^+) *m/z* 287 $[M+H]^+$.

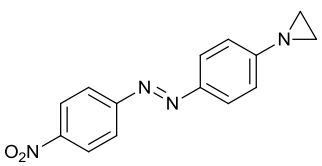
[4-(4-Nitro-phenylazo)-phenyl]-[2-(toluene-4-sulfonyloxy)-ethyl]-ammonium chloride (107)



A novel compound synthesised using a heavily modified procedure.[104] **103** (2.50 g, 9.20 mmol, 1.0 eq), purified tosyl chloride (27.8 g, 92.0 mmol, 10 eq) and DMAP (1.12 g, 9.20 mmol, 1.0 eq) were placed in a round bottom flask. Pyridine (150 mL) cooled to -20 ^{o}C was added *via* cannula. The mixture was stirred at -20 ^{o}C (ethylene glycol / EtOH / $CO_{2\,(s)}$) for 6 h, then quenched with MeOH (100 mL) and the solvent removed by distillation. The solid was purified by column chromatography (10% acetone in petrol). To give a solid contaminated with ditosylate. The solid was dissolved in a minimum volume of anhydrous benzene and hydrogen chloride in diethyl ether was added dropwise until a red solid precipitated.

The solid was isolated by filtration and found to contain 17% of the HCl salt of **103** (331 mg, 8%). m.p. 110 ^{o}C (dec.); R_f = 0.25; IR (thin film) 2813, 1614, 1557, 1508, 1392, 1336, 1259, 1167, 1142, 1101, 1010, 812, 661 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 2.22 (3H, s, ArC*H*$_3$), 3.38 (2H, t, *J* = 5.3, C*H*$_2$), 4.03 (2H, t, *J* = 5.3, C*H*$_2$), 6.57 (2H, d, *J* = 9.0, Ar*H*), 7.27 (2H, d, *J* = 8.1, Ar*H*), 7.57 – 7.68 (4H, m, Ar*H*), 7.82 (2H, d, *J* = 9.0, Ar*H*), 8.26 (2H, d, *J* = 9.1, Ar*H*); ^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ 21.0 (CH_3), 41.0 (CH_2), 68.5 (CH_2), 122.8 (CH), 125.0 (CH), 125.5 (CH), 127.6 (CH), 128.3 (CH), 130.1 (CH), 131.8 (C), 143.2 (C), 144.7 (C), 146.8 (C), 153.0 (C), 156.0 (C); MS (ES$^+$) *m/z* 441 $[M+H]^+$; HRMS (ES$^+$) calcd. For $C_{21}H_{20}N_4O_5SNa$ = 463.1047 $[M+Na]^+$, found 463.1052.

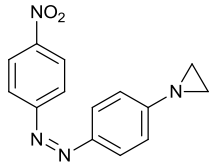
trans-(4-Aziridin-1-yl-phenyl)-(4-nitro-phenyl)-diazene (_trans_-90)



A previously reported compound[94] with limited data synthesised using a novel method. 60% NaH in mineral oil (42 mg, 1.1 mmol, 5.0 eq) was placed under nitrogen, washed with dry petrol (3 x 1 mL) and dried *in vacuo*. **107** (100 mg, 0.21 mmol, 1.0 eq) was dissolved in DMF (10 mL), cooled to 0 ^{o}C, then transferred *via* cannula to the washed NaH and stirred at 0 ^{o}C for 3 h. The mixture was quenched with NH_4Cl (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organics were washed with water (6 x 15 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (10% EtOAc / pet ether + 1% triethylamine) yielded **90** as a shiny orange solid (56 mg, 28%). R_f = 0.25 (10% EtOAc in petroleum ether + 1% triethylamine); IR (thin film) 2994, 1598, 1514, 1344, 1141, 1105, 851 cm^{-1}; UV λ_{max}: 262, 381, 391 nm; ^{1}H NMR (500 MHz, Toluene-*d*$_8$) δ 1.66

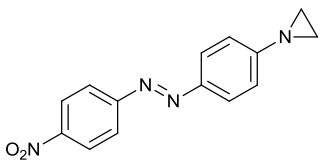
(4H, s, NCH_2), 6.78 (2H, d, *J* = 8.7, Ar*H*), 7.59 (2H, d, *J* = 9.0, Ar*H*), 7.85 (2H, d, *J* = 9.0, Ar*H*), 7.88 (2H, d, *J* = 8.7, Ar*H*); ^{13}C NMR (125 MHz, Toluene-d_8) δ 27.0 (CH_2), 121.1 (CH), 122.7 (CH), 124.2 (CH), 124.8 (CH), 148.1 (C), 148.3 (C), 155.6 (C), 159.6 (C); MS (ES^+) *m/z* 291 $[M+Na]^+$; HRMS (ES^+) calc. for $C_{14}H_{12}N_4NaO_2$ = 291.0852, found 291.0857.

cis-(4-Aziridin-1-yl-phenyl)-(4-nitro-phenyl)-diazene (_cis_-90)



A novel compound synthesised using standard photochemical isomerisation techniques. *trans*-**90** (6 mg, 0.012 mmol) was dissolved in toluene-d_8 (0.6 mL) then filtered into an NMR tube. The tube was suspended at the front of a 2 L beaker containing ice / water. The tube was irradiated with a 125 W medium pressure mercury lamp through a window of glass bandpass filter focused around 390 nm (Schott FSQ-UG1 UV bandpass filter). After being irradiated for 3 h the sample was removed and stored in ice until immediate NMR experiments could be performed. ^{1}H NMR (400 MHz, Toluene-d_8) δ 1.56 (4H, s, NCH_2), 6.32 (2H, d, *J* = 8.8, Ar*H*), 6.47 (2H, d, *J* = 8.8, Ar*H*), 6.64 (2H, d, *J* = 8.8, Ar*H*), 7.59 (2H, d, *J* = 8.8, Ar*H*).

trans-(4-Aziridin-1-yl-phenyl)-(4-nitro-phenyl)-diazene (_trans_-90)



An NMR tube containing *cis*-**90** (6 mg, 0.012 mmol) in toluene-d_8 (0.6 mL) was immersed in an oil bath at 60 ^{o}C for 10 minutes resulting in complete regeneration of *trans*-**90**. The process of photochemical conversion and thermal reconversion was repeated three times in succession with no losses in conversion or degradation of the compounds. In fact over a period of weeks and many switching cycles very little degradation was observed.

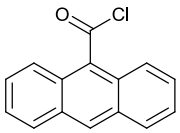
3.3 Photoactivated Biologically Relevant β-lactams Experimental

3.3.1 Biological Testing Procedures

The agar plates were prepared using the following method. A 1% agar solution was warmed and 10 mL poured into each petri dish under a filtered atmosphere, and allowed to set overnight. The following day, two tubes (5 mL) of top agar (0.5%) were melted in a water bath, allowed to reach body temperature and inoculated with either *B.Subtilis* or *E.Coli*. Before the agar set it was poured evenly over the set agar plate to form one continuous thin layer.

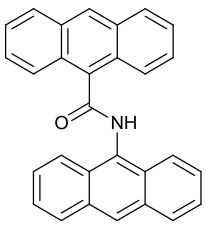
The compounds to be tested were dissolved in DMSO (20 μL) at various loadings up to 500 μg. The 20 μL aliquots were then placed on filter paper disks using an Eppendorf micropipette. The disks containing the test compounds, DMSO (20 μL) and ampicillin (20 μg) in water (20 μL) were placed on top of the set top agar in a predetermined pattern. The plates were then incubated overnight at 37 ^{o}C and the bacterial lawn growth observed.

9-Anthroyl chloride (142)



A known compound synthesised using a published procedure.[183] Anthracene-9-carboxylic acid **141** (2.00 g, 9.00 mmol, 1.0 eq) was suspended in thionyl chloride (9.80 g, 83.0 mmol, 9.2 eq). The mixture was heated to reflux overnight then cooled to room temperature and concentrated *in vacuo*. The solid was washed twice with diethyl ether (2 mL then 12 mL) then the organics concentrated *in vacuo* yielding **142** as a yellow solid (1.68 g, 78%) This solid was very unstable and was therefore used immediately. IR (thin film) 3053, 1777, 1041, 864, 782, 719 cm^{-1}.

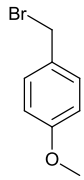
Anthracene-9-carboxylic acid anthracen-9-ylamide (136)



A reported compound but with limited data, synthesised using the documented procedure.[162] To 9-aminoanthracene **59** (1.36 g, 7.00 mmol, 1.0 eq) and 9-anthroyl chloride (1.70 g, 7.00 mmol, 1.0 eq) was added toluene (76 mL) and pyridine (2.5 mL) and the resulting mixture was heated to reflux overnight. The reaction mixture was cooled and the precipitate filtered off. The remaining solid was washed well with 5% HCl then dried ($MgSO_4$) and concentrated *in vacuo*. The crude solids were combined and recrystallised from benzene to yield **136** as a light yellow powder (876 mg, 32%). m.p. 285 – 287 ^oC (Benzene) (Lit. 302 – 304 ^oC); IR (thin film) 3261, 3044, 1649, 1480, 1214, 879, 726 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.70 (8H, m, Ar*H*), 8.07 – 8.16 (5H, m, N*H*, Ar*H*), 8.42 (2H, d, *J* = 8.8, Ar*H*), 8.55 (1H, s, Ar*H*), 8.60 (2H, d, *J* = 8.8, Ar*H*), 8.63 (1H, s, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 123.3 (CH),

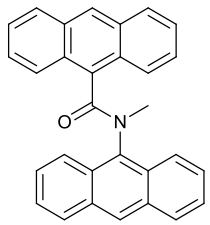
125.3 (CH), 125.5 (CH), 125.8 (CH), 126.8 (CH), 127.2 (CH), 127. 4 (C), 127.7 (CH), 128.4 (C), 128.6 (C), 128.9 (CH), 129.0 (CH), 131.9 (C), 148.3 (CH), 148.6 (C), 169.2 (C=O); MS (ES^+) *m/z* 398 $[M+H]^+$, 420 $[M+Na]^+$; HRMS (ES^+) calcd. For $C_{29}H_{19}NNaO$ = 420.1359 $[M+Na]^+$, found 420.1363.

4-Methoxybenzyl bromide (184)



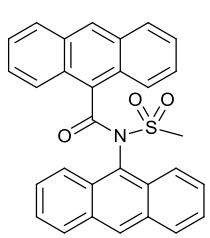
A compound synthesised using a reported procedure.[184] To a solution of 4-methoxybenzyl alcohol (7.10 g, 52.0 mmol, 3.0 eq) in dichloromethane (75 mL) at 0 ^oC was slowly added phosphorus tribromide (4.42 g, 16.5 mmol, 1.0 eq) and the mixture stirred for 12 h. The mixture was poured into saturated sodium bicarbonate (150 mL) and extracted with dichloromethane (3 x 50 mL), dried ($MgSO_4$) then concentrated *in vacuo*. The resulting yellow oil **183** was used without further purification (10.4 g, 99%). ^1H NMR (400 MHz, $CDCl_3$) δ 3.84 (3H, s, C*H*$_3$), 4.54 (2H, s, C*H*$_2$), 6.91 (2H, d, *J* = 8.6, Ar*H*), 7.37 (2H, d, *J* = 8.6, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.5 (CH_2), 55.4 (CH_3), 114.6 (CH), 129.8 (C), 130.2 (CH), 159.7 (C); MS (ES^+) *m/z* 201 $[^{79}BrM+H]^+$, 203 $[^{81}BrM+H]$.

Anthracene-9-carboxylic acid anthracen-9-yl-methyl-amide (143)



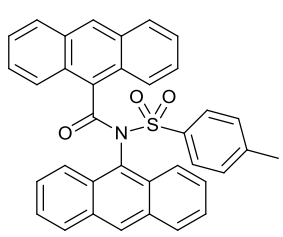
A novel compound prepared using standard alkylation procedures. Sodium hydride 60% in mineral oil (57 mg, 1.41 mmol, 2.0 eq) was washed with dry pentane (2 x 1 mL) and dried *in vacuo*. It was then suspended in THF (12.8 mL) and cooled to 0 ^{o}C. A solution of **136** (280 mg, 0.71 mmol, 1.0 eq) in THF (11.2 mL) was also cooled to 0 ^{o}C then added dropwise. After stirring for 30 minutes at 0 ^{o}C methyl iodide (120 mg, 53 µl, 0.85 mmol, 1.2 eq) was added dropwise. The mixture was allowed to warm and stirred overnight. The reaction mixture was quenched with water (100 mL) and extracted with dichloromethane (3 x 60 mL). The combined organics were washed with water (60 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification was attempted by flash chromatography (10% EtOAc in petrol) however, spontaneous isomerisation in ambient light led to poor poor mass recovery. R_f = 0.44 (20% EtOAc in petrol); IR (thin film) 3044, 2360, 1750, 1453, 1379, 1291, 1015, 788, 722, 719 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.18 (3H, s, C*H*$_3$), 7.57 – 7.64 (4H, m, Ar*H*), 7.69 – 7.78 (4H, m, Ar*H*), 8.15 (2H, d, *J* = 8.4, Ar*H*), 8.16 (2H, d, *J* = 8.4, Ar*H*), 8.47 (2H, d, *J* = 8.9, Ar*H*), 8.56 – 8.64 (4H, m, Ar*H*); MS (ES^{+}) *m/z* 412 $[M+H]^{+}$.

_N_-(Anthracene-9-carbonyl)-_N_-anthracen-9-yl-methanesulfonamide (144)



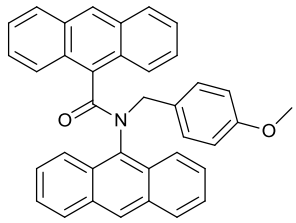
A novel compound prepared using standard alkylation procedures. Sodium hydride 60% in mineral oil (10 mg, 0.25 mmol, 2.0 eq) was washed with dry pentane (2 x 1 mL) and dried *in vacuo*. It was then suspended in THF (2.3 mL) and cooled to 0 ^{o}C. A solution of **136** (50 mg, 0.13 mmol, 1.0 eq) in THF (2.5 mL) was also cooled to 0 ^{o}C then added dropwise. After stirring for 30 minutes at 0 ^{o}C, mesyl chloride (22 mg, 0.19 mmol, 1.2 eq) was added. The mixture was allowed to warm and stirred overnight. The reaction mixture was quenched with water (25 mL) and extracted with dichloromethane (3 x 15 mL). The combined organics were washed with water (15 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The product was purified by column chromatography through silica gel (39% dichloromethane, 1% acetone in petrol) then triturated in diethyl ether. The product was found to isomerise in ambient light during purification resulting in poor mass recovery (20 mg, 32%). R_f = 0.24 (39% dichloromethane, 1% acetone in petrol); MS (ES^+) *m/z* 498 [$M+H^+$]

_N_-(Anthracene-9-carbonyl)-_N_-anthracen-9-yl-4-methyl-benzenesulfonamide (145)



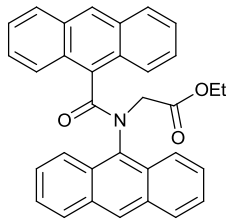
A novel compound prepared using standard alkylation procedures. Sodium hydride 60% in mineral oil (10 mg, 0.25 mmol, 2.0 eq) was washed with dry pentane (2 x 1 mL) and dried *in vacuo*. It was then suspended in THF (2.3 mL) and cooled to 0 ^{o}C. A solution of **136** (50 mg, 0.13 mmol, 1.0 eq) in THF (2.5 mL) was also cooled to 0 ^{o}C then added dropwise. After stirring for 15 minutes at 0 ^{o}C, tosyl chloride (30 mg, 0.15 mmol, 1.2 eq) was added. The mixture was allowed to warm to rt and stirred overnight. The reaction mixture was quenched with water (15 mL) and extracted with dichloromethane (3 x 5 mL). The combined organics were washed with water (5 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification was attempted by flash chromatography (10% EtOAc in petrol) however, spontaneous isomerisation in ambient light led to poor poor mass recovery. R_f = 0.31 (10% EtOAc in petrol); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.58 (3H, s, C*H*$_3$), 7.15 – 7.22 (2H, m, Ar*H*), 7.53 – 7.69 (8H, m, Ar*H*), 8.04 – 8.15 (4H, m, Ar*H*), 8.32 – 8.45 (4H, m, Ar*H*), 8.51 – 8.64 (4H, m, Ar*H*); MS (ES^+) *m/z* 574 [$M+Na^+$].

Anthracene-9-carboxylic acid anthracen-9-yl-(4-methoxy-benzyl)-amide (146)



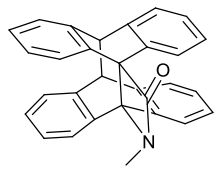
A novel compound prepared using standard alkylation procedures. Sodium hydride 60% in mineral oil (33 mg, 0.76 mmol, 2.0 eq) was washed with dry pentane (2 x 1 mL) and dried *in vacuo*. It was then suspended in THF (7 mL) and cooled to 0 ^{o}C. A solution of **136** (150 mg, 0.38 mmol, 1.0 eq) in THF (7.5 mL) was also cooled to 0 ^{o}C then added dropwise. After stirring for 30 minutes at 0 ^{o}C, 4-methoxybenzyl bromide (115 mg, 0.57 mmol, 1.2 eq) was added dropwise. The mixture was allowed to warm to rt and stirred for 3 days. The reaction mixture was quenched with water (25 mL) and extracted with dichloromethane (3 x 15 mL). The combined organics were washed with water (15 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The product was used without further purification due to spontaneous isomerisation in ambient light. R_f = 0.32 (39% dichloromethane, 1% acetone in petrol); MS (ES^+) *m/z* 518 [$M+H^+$].

[(Anthracene-9-carbonyl)-anthracen-9-yl-amino]-acetic acid ethyl ester (147)



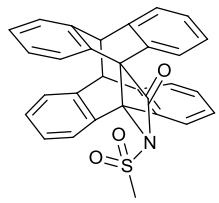
A novel compound prepared using standard alkylation procedures. The entire preparation and purification of this compound was carried out in a dark room using only red light. Sodium hydride 60% in mineral oil (39 mg, 0.95 mmol, 2.0 eq) was washed with dry pentane (2 x 3 mL) and dried *in vacuo*. It was then suspended in THF (8.4 mL) and cooled to 0 ^{o}C. A solution of **136** (188 mg, 0.47 mmol, 1.0 eq) in THF (9 mL) was also cooled to 0 ^{o}C then added dropwise. After stirring for 30 minutes at 0 ^{o}C, ethyl bromoacetate (119 mg, 0.71 mmol, 1.2 eq) was added dropwise. The mixture was allowed to warm and stirred overnight in the dark. Methanol (0.2 mL) was added and the mixture concentrated *in vacuo*. The resulting solid was dissolved in dichloromethane (20 mL) and washed with water (3 x 7 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The solid was purified by column chromatography (39.5% dichloromethane, 0.5% acetone in petrol) then (0.1% methanol in dichloromethane) yielding a yellow / green solid (46 mg, 20%) limited data was obtained due to instability in ambient light. R_f = 0.34 (39% dichloromethane, 1% acetone in petrol); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.70 (1.77H, t, *J* = 7.2, C*H*$_3$, minor), 1.38 (3H, t, *J* = 7.1, C*H*$_3$, major), 3.46 (1.1H, q, *J* = 7.2, C*H*$_2$CH$_3$, minor), 4.22 (1.1H, s, C*H*$_2$), 4.38 (2H, q, *J* = 7.1, C*H*$_2$CH$_3$, major), 4.99 (2H, s, C*H*$_2$, major), 7.02 – 7.18 (8H, m, Ar*H*), 7.33 – 7.45 (4H, m, Ar*H*), 7.51 – 7.59 (2.31H, m, Ar*H*), 7.62 – 7.73, (4.28H, m, Ar*H*), 8.04 – 8.12 (2.26H, m, Ar*H*), 8.29 (2H, d, *J* = 8.8, Ar*H*), 8.42 (1.1H, d, *J* = 8.7, Ar*H*), 8.46 (2H, d, *J* = 8.8, Ar*H*), 8.53 – 8.60 (2.11H, m, Ar*H*); MS (ES$^+$) *m/z* 484 [M+H]$^+$.

2a,7:8,12b-Di-o-benzenodibenzo[3,4:7,8]cycloocta[1,2-b]azet-2(1*H*)-one,7,8-dihydro-1-methyl-(8CI) (148)



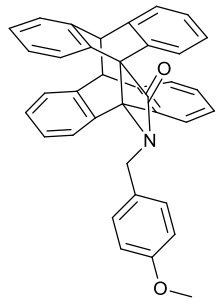
A novel compound prepared using standard photochemical isomerisation conditions. **143** (25 mg, 0.061 mmol) was transferred to a Shlenk tube using a small quantity of dichloromethane (5 mL) then dried *in vacuo*. Benzene (50 mL) was added and the solution degassed by freeze pump thaw cycles under argon. Sonication was applied during thawing and argon bubbled through for 10 minutes after thawing. This process was repeated 5 times. The solution was then irradiated with a 125 W medium pressure Hg lamp for 1 h. The paler solution was then concentrated *in vacuo*. Purification by flash chromatography (6:4:0.1 petrol:dichloromethane:acetone) and trituration with diethyl ether yielded **148** as a white solid (14 mg, 56%). m.p. 280 ^{o}C (dec); R_f 0.26 (6:4:0.1 petrol:dichloromethane:acetone); IR (thin film) 2364, 1751, 1453, 1378, 1292, 1016, 789, 722, 701 cm^{-1}: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.50 (3H, s, C*H*$_3$), 4.56 (1H, d, *J* = 11.0, Ar_2CH), 4.65 (1H, d, *J* = 11.0, Ar_2CH), 6.85 – 6.97 (12H, m, Ar*H*), 6.99 – 7.12 (2H, m, Ar*H*), 7.18 – 7.26 (2H, m, Ar*H*); ^{13}C NMR (100 MHz, DMSO-d_6) δ 28.2 (CH_3), 51.1 (CH), 51.8 (CH), 122.4 (CH), 123.6 (CH), 125.6 (CH), 125.8 (CH), 126.4 (CH), 126.5 (CH), 127.4 (CH), 127.8 (CH), 138.8 (C), 140.0 (C), 141.6 (C), 142.1 (C) 2 x (C), 1 x (C=O) not observed; MS (ES$^+$) *m/z* 434 [M+Na]$^+$; HRMS (ES$^+$) calcd. For $C_{30}H_{21}NNaO$ = 434.1515 [M+Na]$^+$, found 434.1510.

2a,7:8,12b-Di-o-benzenodibenzo[3,4:7,8]cycloocta[1,2-b]azet-2(1*H*)-one,7,8-dihydro-1-(methanesulfonamide)-(8CI) (149)



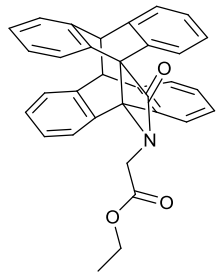
A novel compound prepared using standard photochemical isomerisation conditions. **144** (19.7 mg, 0.041 mmol) was transferred to a Shlenk tube using dichloromethane (5 mL) then dried *in vacuo*. Benzene (50 mL) was then added and the solution degassed by freeze pump thaw under argon. Sonication was applied during thawing and argon bubbled through for 10 minutes after thawing. This process was repeated 5 times. The solution was then irradiated by a 125 W medium pressure Hg lamp for 1 h. The paler solution was then concentrated *in vacuo*. Purification by flash chromatography (6:4:0.05 petrol:dichloromethane:acetone) and trituration with diethyl ether yielded **149** as a white solid (13 mg, 65%). m.p. 200 ^{o}C (dec.); R_f = 0.28 (6:4:0.05 petrol:dichloromethane:acetone); IR (thin film) 3036, 2927, 1746, 1454, 1349, 1165, 724 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.86 (3H, s, C*H*$_3$), 4.61 (1H, d, *J* = 11.1, C*H*), 4.68 (1H, d, *J* = 11.1, C*H*), 6.85 – 7.05 (12H, m, Ar*H*), 7.07 – 7.14 (2H, m, Ar*H*), 7.26 – 7.32 (2H, m, Ar*H*); ^{13}C NMR (175 MHz, $CDCl_3$) δ 43.4 (CH_3), 52.4 (CH), 52.9 (CH), 78.4 (C), 84.4 (C), 123.5 (CH), 124.2 (CH), 126.27 (CH), 126.31 (CH), 127.3 (CH), 127.4 (CH), 127.5 (CH), 128.0 (CH), 136.8 (C), 138.1 (C), 140.6 (C), 141.6 (C), 165.5 (C=O); MS (ES$^+$) *m/z* 498 $[M+Na]^+$; HRMS (ES$^+$) Calc. For $C_{30}H_{21}NNaO_3S$ =498.1134 $[M+Na]^+$, Found = 498.1133.

2a,7:8,12b-Di-o-benzenodibenzo[3,4:7,8]cycloocta[1,2-b]azet-2(1*H*)-one,7,8-dihydro-1-(4-methoxy-benzyl)-(8CI) (151)



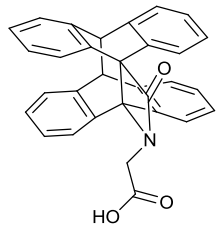
A novel compound prepared using unusual photochemical isomerisation conditions. **146** (19.7 mg, 0.041 mmol) was dissolved in laboratory grade chloroform (200 mL) and stirred in a direct sunlight for 4 h. The paler solution was then concentrated *in vacuo*. Purification by flash chromatography (6:4:0.05 petrol:dichloromethane:acetone) and trituration with diethyl ether yielded **151** as a white solid (70 mg, 36% over 2 steps). m.p. 200 ^{o}C (dec.); R_f = 0.34 (6:4:0.1 petrol:dichloromethane:acetone); IR (thin film) 1744, 1510, 1454, 1248, 1028, 791, 722 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.89 (3H, s, OC*H*$_3$), 4.56 (1H, d, *J* = 10.9, C*H*), 4.65 (1H, d, *J* = 10.9, C*H*), 4.93 (2H, s, C*H*$_2$) 6.75 – 6.95 (12H, m, Ar*H*), 7.00 (4H, d, *J* = 8.5, Ar*H*), 7.21 – 7.27 (2H, m, Ar*H*), 7.63 (2H, d, *J* = 8.5, Ar*H*); ^{13}C NMR (175 MHz, $CDCl_3$) δ 46.9 (CH_2), 52.6 (CH), 53.2 (CH_3), 55.3 (CH), 77.5 (C), 79.0 (C), 114.3 (CH), 123.4 (CH), 124.6 (CH), 125.9 (CH), 126.0 (CH), 126.5 (CH), 126.6 (CH), 127.4 (CH), 127.6 (CH), 129.8 (C), 130.2 (CH), 138.9 (C), 140.0 (C), 141.5 (C), 141.7 (C), 159.2 (C), 167.7 (C=O); MS (ES$^+$) *m/z* 518 [M+H]$^+$, 540 [M+Na]$^+$; HRMS (ES$^+$) Calc. For $C_{37}H_{27}NNaO_2$ = 540.1934[M+Na]$^+$, Found = 540.1946.

2a,7:8,12b-Di-o-benzenodibenzo[3,4:7,8]cycloocta[1,2-b]azet-2(1*H*)-one,7,8-dihydro-1-(acetic acid ethyl ester)-(8CI) (152)



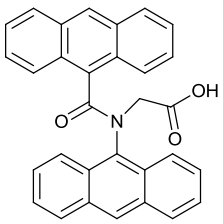
A novel compound prepared using standard photochemical isomerisation conditions. Crude **147** (69 mg, 0.14 mmol) was dissolved in dichloromethane (10 mL) and 5 mL added to two schlenk tubes (100 mL) then dried *in vacuo*. Benzene (50 mL) was added to each and the solution degassed by freeze pump thaw under argon. Sonication was applied during thawing and argon bubbled through for 10 minutes after thawing. This process was repeated 5 times. The solution was then irradiated by a 125 W medium pressure Hg lamp for 1 h. The paler solution was then concentrated *in vacuo*. Purification by flash chromatography (6:4:0.05 petrol:dichloromethane:acetone) and trituration with diethyl ether yielded **152** as a white solid (60 mg, 33% over 2 steps). m.p. 200 ^{o}C (dec.); R_f = 0.22 (6:4:0.05 petrol:dichloromethane:acetone); IR (thin film) 3038, 1746, 1470, 1383, 1202, 790, 724 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (3H, t, *J* = 7.1, CH_2CH_3), 4.46 (2H, q, *J* = 7.1, CH_2CH_3), 4.49 (2H, s, NCH_2CO), 4.58 (1H, d, *J* = 11.1, C*H*), 4.66 (1H, d, *J* = 11.1, C*H*), 6.85 – 6.98 (10H, m, Ar*H*), 7.00 – 7.06 (2H, m, Ar*H*), 7.08 – 7.14 (2H, m, Ar*H*), 7.25 – 7.32 (2H, m, Ar*H*); ^{13}C NMR (175 MHz, $CDCl_3$) δ 14.2 (CH_3), 44.5 (CH_2), 52.6 (CH), 53.1 (CH), 62.1 (CH_2), 77.9 (C), 78.0 (C), 122.6 (CH), 124.7 (CH), 126.0 (CH), 126.1 (CH), 126.2 (CH), 126.6 (CH), 126.8 (CH), 127.5 (CH), 127.6 (CH), 138.5 (C), 140.1 (C), 141.6 (C), 166.9 (C=O), 167.6 (C=O); MS (ES$^+$) *m/z* 484 $[M+H]^+$, 506 $[M+Na]^+$; HRMS (ES$^+$) Calc. For $C_{33}H_{25}NNaO_3$ = 506.1727 $[M+Na]^+$, Found = 506.1734.

2a,7:8,12b-Di-o-benzenodibenzo[3,4:7,8]cycloocta[1,2-b]azet-2(1*H*)-one,7,8-dihydro-1-(acetic acid)-(8CI) (154)



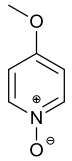
A novel compound prepared using standard hydrolysis conditions. **152** (90 mg, 0.19 mmol) was dissolved in a 50:50 mixture of THF and water (4 mL), powdered NaOH (15 mg, 0.38 mmol, 2.0 eq) was added, and the mixture stirred for 2.5 h. The solution was diluted with water (10 mL) and acidified with 1M HCl until pH = 1 (litmus). This was then extracted with dichloromethane (3 x 15 mL), the combined organics were washed with water (10 mL), dried ($MgSO_4$) and concentrated *in vacuo* yielding **154** as a white solid which did not require further purification (72 mg, 83%). m.p. 200 ^oC (dcc.); IR (thin film) 3042, 2360, 1764, 1715, 1453, 1193, 788, 725, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.57 (2H, s, C*H*$_2$), 4.66 (1H, d, *J* = 11.1, C*H*), 4.73 (1H, d, *J* = 11.1, C*H*), 6.85 (4H, m, Ar*H*), 6.89 (4H, m, Ar*H*), 7.01 (2H, m, Ar*H*), 7.05 (2H, m, Ar*H*), 7.15 (2H, m, Ar*H*), 7.18 (2H, m, Ar*H*); ^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ 44.1 (CH_2), 51.3 (CH), 51.7 (CH), 76.6 (C), 77.0 (C), 122.8 (CH), 123.8 (CH), 125.56 (CH), 125.64 (CH), 126.4 (CH), 127.2 (CH), 127.7 (CH), 138.7 (C), 140.1 (C), 141.5 (C), 142.1 (C), 165.7 (C=O), 169.3 (C=O); MS (ES^+) *m/z* 478 $[M+Na]^+$; HRMS (ES^+) Calc. For $C_{31}H_{21}NNaO_3$ = 4748.141 $[M+Na]^+$, Found = 478.1419 .

[(Anthracene-9-carbonyl)-anthracen-9-yl-amino]-acetic acid (155)



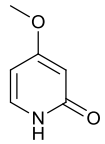
A novel compound synthesised using standard hydrolysis conditions. In a dark room, **147** (46 mg, 0.095 mmol, 1.0 eq) was dissolved in a 1:1 mixture of THF:water (2 mL). Sodium hydroxide (8 mg, 0.19 mmol, 2.0 eq) was added and the mixture stirred at room temperature overnight. No reaction was observed by TLC so the mixture was heated to reflux for 6 h then allowed to cool to room temperature. The solution was diluted with water (10 mL) and acidified with 1M HCl until pH = 1 (litmus). This was then extracted with dichloromethane (3 x 15 mL), the combined organics were washed with water (10 mL), dried ($MgSO_4$) and concentrated *in vacuo* yielding **154** as a yellow solid which did not require further purification (19 mg, 44%). Limited data was obtained due to poor stability. ^{1}H NMR (300 MHz, Acetone d_6) δ 5.13 (2H, s, CH_2), 7.17 – 7.37 (8H, m, Ar*H*), 7.51 – 7.71 (4H, m, Ar*H*), 8.01 (1H, s, Ar*H*), 8.07 (1H, s, Ar*H*), 8.49 – 8.57 (2H, m, Ar*H*), 8.83 (2H, d, *J* = 8.8, Ar*H*); MS (ES^+) *m/z* 456 $[M+H]^+$.

4-Methoxypyridine *N*-oxide (165)



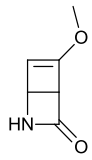
A known compound synthesised using a published procedure.[185] Sodium (1.50 g, 65.2 mmol, 2.0 eq) was dissolved in MeOH (100 mL) at 0 ^{o}C. When hydrogen evolution had stopped 4-nitropyridine *N*-oxide (5.01 g, 35.8 mmol, 1.0 eq) was added and the mixture heated to reflux overnight. The reaction mixture was cooled to room temperature and quenched carefully with saturated ammonium chloride solution (30 mL) then extracted with $CHCl_3$ (4 x 100 mL). The combined organics were washed with water (50 mL), brine (50 mL) then dried ($MgSO_4$) and concentrated *in vacuo* yielding **165** a white solid which was used without further purification, (3.95 g, 90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.85 (3H, s, C*H*$_3$), 6.79 (2H, d, *J* = 7.7, Ar*H*), 8.11 (2H, d, *J* = 7.7, Ar*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 56.2 (CH_3), 111.9 (CH), 140.2 (CH), 158.0 (C); MS (ES^+) *m/z* 126 $[M+H]^+$, 148 $[M+Na]^+$.

4-Methoxy-2-pyridone (167)



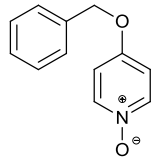
A known compound synthesised using a known procedure.[186] 4-methoxypyridine *N*-oxide (2.48 g, 19.8 mmol) was dissolved in acetic anhydride (80 mL) and heated to reflux for 6 h. The solvent was removed *in vacuo* and the intermediate purified by kugelrohr distillation (90 ^{o}C, 2 mbar). The product was dissolved in methanol (10 mL) and water (10 mL) and stirred at room temperature for 1 h. The solvent was removed *in vacuo* and the resulting solid recrystallised from acetonitrile producing **167** as colourless flakes (960 mg, 39%). IR (thin film) 3078, 2943, 2834, 2361, 2341, 1648, 1576, 1483, 1427, 1341, 1209, 1023, 851, 777 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.77 (3H, s, C*H*$_3$), 5.87 (1H, d, *J* = 2.5, Ar*H*), 5.96 (1H, dd, *J* = 7.3, 2.5, Ar*H*), 7.20 (1H, d, *J* = 7.3, Ar*H*), 12.98 (1H, s, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.5 (CH_3), 97.2 (CH), 101.3 (CH), 134.7 (CH), 167.5 (C), 169.9 (C); MS (ES^{+}) *m/z* 126 $[M+H]^{+}$, 148 $[M+Na]^{+}$.

5-Methoxy-2-aza-bicyclo[2.2.0]hex-5-en-3-one (168)



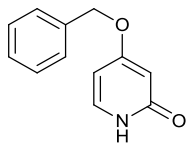
A known compound synthesised using a modified procedure.[186] Anhydrous acetonitrile (500 mL) was degassed by freeze pump thaw then added *via* cannula to 4-methoxy-2-pyridine (150 mg, 1.20 mmol) in a large Schlenk tube. This solution was stirred and irradiated with a 125 W medium pressure Hg lamp through a < 355 nm cut off filter for 1 day. After irradiation the solution was concentrated *in vacuo* then purified by column chromatography (40 – 50% EtOAc in petrol) yielding **168** as a white solid (150 mg, quant.). R_f = 0.26 (50% EtOAc in petrol). IR (thin film) 1744, 1246,1056 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 3.70 (3H, s, CH_3), 4.16 – 4.21 (1H, m, C*H*), 4.23 (1H, d, *J* = 2.5, C*H*), 5.18 (1H, d, *J* = 1.1, C*H*), 7.37 (1H, s, N*H*); ^{13}C NMR (100 MHz, acetone-d_6) δ 42.9 (CH), 57.1 (CH_3), 61.4 (CH), 103.3 (CH), 161.4 (C), 170.5 (C=O); MS (ES^+) *m/z* 126 $[M+H]^+$, 148 $[M+Na]^+$, 273 $[2M+Na]^+$.

4-Benzyloxypyridine *N*-oxide (169)



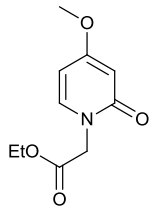
A previously reported compound synthesised using a modified version of a reported procedure.[185] Sodium (0.38 g, 16.3 mmol, 2.0 eq) was dissolved in benzyl alcohol (25 mL) at 0 ^{o}C. When hydrogen evolution had stopped, 4-nitropyridine *N*-oxide (1.14 g, 8.15 mmol, 1.0 eq) was added and the mixture heated to reflux overnight. The reaction mixture was cooled to room temperature and quenched carefully with saturated ammonium chloride solution (10 mL) then extracted with $CHCl_3$ (4 x 25 mL). The combined organics were washed with water (10 mL), brine (10 mL) then dried ($MgSO_4$) and concentrated *in vacuo* yielding a yellowish solid which was purified by trituration with diethyl ether giving **169** as a white powder (850 mg, 52%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.10 (2H, s, C*H*$_2$), 6.86 (2H, d, *J* = 7.7, Ar*H*), 7.29 – 7.51 (5H, m, Ar*H*), 8.11 (2H, d, *J* = 7.7, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 69.8 (CH_2), 113.6 (CH), 129.2 (CH), 129.4 (CH), 129.5 (CH), 136.7 (C), 140.4 (CH), 163.4 (C); MS (ES^+) *m/z* 202 $[M+H]^+$, 224 $[M+Na]^+$, 403 $[2M+H]^+$, 425 $[2M+Na]^+$.

4-Benzyloxy-2-pyridone (170)



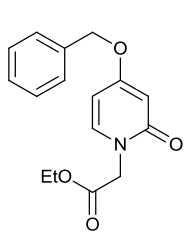
A known compound synthesised using a modified procedure.[186] 4-benzyloxypyridine *N*-oxide (0.85 g, 4.1 mmol) was dissolved in acetic anhydride (28 mL) and heated to reflux for 6 h. The solvent was removed *in vacuo* and the intermediate purified by kugelrohr distillation (110 ^{o}C, 2 mbar). The product was dissolved in methanol (5 mL) and water (5 mL) and stirred at room temperature for 1 h. The solvent was removed *in vacuo* and the resulting solid recrystallised from acetonitrile producing **170** as colourless flakes (440 mg, 50%). IR (thin film) 2786, 2360, 1623, 1450, 1201, 996, 819, 776, 739, 694 cm^{-1}; ^{1}H NMR (300 MHz, MeOD) δ 5.10 (2H, s, C*H*$_3$), 5.99 (1H, d, *J* = 7.4, Ar*H*), 6.17 (1H, dd, *J* = 7.4, 2.5, Ar*H*), 7.27 – 7.47 (6H, m, Ar*H*); ^{13}C NMR (125 MHz, Acetone-d_6) δ 69.7 (CH_2), 98.0 (CH), 99.6 (CH), 127.8 (CH), 128.1 (CH), 128.5 (CH), 134.9 (CH), 136.3 (C), 164.4 (C), 168.1 (C); MS (ES$^+$) *m/z* 224 [M+Na]$^+$, 425 [2M+Na]$^+$; HRMS (ES$^+$) Calc. For $C_{12}H_{12}NO_2$ = 202.0863 [M+H]$^+$, Found 202.0868; CHN Calc. For $C_{12}H_{11}NO_2$ C, 71.63 H, 5.51 N, 6.96%, Found C, 71.54 H, 5.50 N, 6.92%.

(4-Methoxy-2-oxo-2*H*-pyridin-1-yl) acetic acid ethyl ester (175)



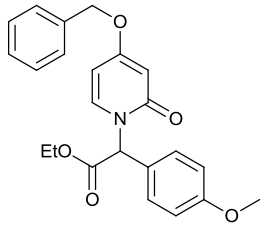
A novel compound synthesised using standard alkylation conditions. 4-Methoxy-2-pyridone (200 mg, 1.60 mmol, 1.0 eq), ethyl bromoacetate (267 mg, 1.60 mmol, 1.0 eq) and potassium carbonate (2.00 g, 16.0 mmol, 10 eq) were dissolved in DMF (4 mL) and stirred at room temperature overnight. The mixture was diluted with ammonium chloride (50 mL) and extracted with dichloromethane (3 x 25 mL). The combined organics were washed with water (6 x 20 mL), brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The resulting solid was then triturated with diethyl ether leaving **175** as a white powder (240 mg, 73%). m.p. 158 - 160 ^oC; IR (thin film) 2360, 1737, 1653, 1592, 1197, 1018, 821, 795 cm^{-1}; ^1H NMR (300 MHz, MeOD) δ 1.27 (3H, t, *J* = 7.1, CH_2CH_3), 3.83 (3H, s, OCH_3), 4.22 (2H, q, *J* = 7.1), 4.66 (2H, s, NCH_2CO), 5.94 (1H, d, *J* = 2.4, Ar*H*), 6.12 (1H, dd, *J* = 7.6, 2.6, Ar*H*), 7.47 (1H, d, *J* = 7.6, Ar*H*); ^{13}C NMR (75 MHz, MeOD) δ 14.4 (CH_3), 51.1 (CH_2), 56.4 (CH_3), 62.7 (CH_2), 97.2 (CH), 102.8 (CH), 140.3 (CH), 165.1 (C), 170.0 (C=O), 170.3 (C=O); MS (ES^+) *m/z* 234 $[M+Na]^+$; HRMS (ES^+) Calc. For $C_{10}H_{13}NNaO_4$ = 234.0737 $[M+Na]^+$, Found 234.0744; CHN Calc. For $C_{10}H_{13}NO_4$ C, 56.86 H, 6.20 N, 6.63%, Found C, 56.83 H, 6.18 N, 6.70%.

(4-Benzyloxy-2-oxo-2*H*-pyridin-1-yl) acetic acid ethyl ester (176)



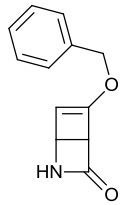
A novel compound synthesised using standard alkylation procedures. 4-benzyloxy-2-pyridone (150 mg, 0.75 mmol, 1.0 eq), ethyl bromoacetate (125 mg, 0.75 mmol, 1.0 eq) and potassium carbonate (956 mg, 7.50 mmol, 10 eq) were dissolved in DMF (3 mL) and stirred at room temperature overnight. The mixture was diluted with ammonium chloride (30 mL) and extracted with dichloromethane (3 x 15 mL). The combined organics were washed with water (6 x 10 mL), brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The resulting solid was then triturated with diethyl ether leaving **176** as a white solid (120 mg, 55%). m.p. 171 - 173 ^oC; IR (thin film) 2361, 1732, 1662, 1603,1221, 1200, 1024, 728 cm^{-1}; ^1H NMR (300 MHz, MeOD) δ 1.27 (3H, t, *J* = 7.1, C*H*$_3$), 4.21 (2H, q, *J* = 7.1, OC*H*$_2$CH$_3$), 4.66 (2H, s, C*H*$_2$), 5.11 (2H, s, C*H*$_2$), 6.03 (1H, d, *J* = 2.7, Ar*H*), 6.18 (1H, dd, *J* = 7.6, 2.7, Ar*H*), 7.30 – 7.52 (6H, m, Ar*H*); MS (ES^+) *m/z* 288 $[M+H]^+$, 310 $[M+Na]^+$; HRMS (ES^+) Calc. For $C_{16}H_{17}NNaO_4$ = 310.1050 $[M+Na]^+$, Found 310.1053; CHN Calc. For $C_{16}H_{17}NO_4$ C, 66.71 H, 5.96 N, 4.88%, Found C, 66.27, H, 5.91 N, 4.88%.

(4-Benzyloxy-2-oxo-2*H*-pyridin-1-yl)-(4-methoxy-phenyl)-acetic acid ethyl ester (177)



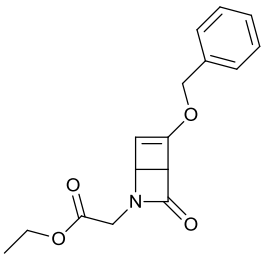
A novel compound synthesised using standard alkylation procedures. 4-benzyloxy-2-pyridone (150 mg, 0.75 mmol, 1.0 eq), **174** (204 mg, 0.75 mmol, 1.0 eq) and potassium carbonate (956 mg, 7.50 mmol, 10 eq) were dissolved in DMF (3 mL) and stirred at room temperature overnight. The mixture was diluted with ammonium chloride (30 mL) and extracted with dichloromethane (3 x 15 mL). The combined organics were washed with water (6 x 10 mL), brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The resulting solid was then triturated with diethyl ether leaving **177** as a white solid (155 mg, 53%). m.p. 144 - 146 ^oC; IR (thin film) 2361, 2343, 1750, 1653, 1198, 1176, 1028, 826, 742 cm^{-1}; ^1H NMR (300 MHz, MeOD) δ 1.25 (3H, t, *J* = 7.1, CH_2CH_3), 3.83 (3H, s, OCH_3), 4.26 (2H, q, *J* = 7.1, CH_2CH_3), 5.10 (2H, s, CH_2Ph), 6.01 – 6.11 (2H, m, Ar*H*), 6.33 (1H, s, C*H*), 6.98 – 7.09 (3H, m, Ar*H*), 7.25 – 7.45 (7H, m, Ar*H*); MS (ES^+) *m/z* 416 $[N+Na]^+$; HRMS (ES^+) Calc. For $C_{22}H_{23}NNaO_5$ = 416.1468 $[M+Na]^+$, Found 416.1480; CHN Calc. For $C_{22}H_{23}NO_5$ C, 70.2 H, 5.89 N, 3.56%, Found C, 69.89 H, 5.90 N, 3.59%.

5-Benzyloxy-2-aza-bicyclo[2.2.0]hex-5-en-3-one (178)



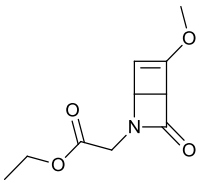
A known compound synthesised using a modified procedure.[186] Anhydrous acetonitrile (250 mL) was degassed by freeze pump thaw then added *via* cannula to 4-methoxy-2-pyridine (80 mg, 0.40 mmol) in a large Schlenk tube. This solution was stirred and irradiated with a 125 W medium pressure Hg lamp through a <355 nm cut off filter for 1 day. After irradiation the solution was concentrated *in vacuo* then purified by column chromatography (30 – 40% EtOAc in petrol) yielding **178** as a white solid (63 mg, 79%). R_f = 0.24 (40% EtOAc in petrol). ^{1}H NMR (400 MHz, acetone-d_6) δ 2.90 (1H, s, N*H*), 4.23 – 4.27 (2H, m, C*H*), 4.96 (1H, d, *J* = 12.0, CH*H*), 4.99 (1H, d, *J* = 12.0, C*H*H), 5.25 (1H, d, *J* = 1.2, =C*H*), 7.35 – 7.48 (5H, m, Ar*H*); ^{13}C NMR (100 MHz, acetone-d_6) 43.2 (CH), 61.6 (CH), 72.2 (CH_2), 104.5 (CH), 128.7 (CH), 129.0 (CH), 129.3 (CH), 137.2 (C), 160.2 (C), 170.5 (C=O); MS (ES^+) *m/z* 202 $[M+H]^+$.

(5-Benzyloxy-3-oxo-2-aza-bicyclo[2.2.0]hex-5-en-2-yl)-acetic acid ethyl ester (179)



A novel compound synthesised using modified photochemical procedures.[186] **176** (60 mg, 0.21 mmol) was dissolved in dry acetonitrile (200 mL) in a large Schlenk tube and degassed by three freeze, pump, thaw cycles under argon. The solution was irradiated with a 125 W medium pressure Hg lamp through a <355 nm cut off filter for 2 days. The solution was then concentrated *in vacuo* and the solid purified by column chromatography (20 – 30% EtOAc in petrol) to yield **179** as a white solid (34 mg, 57%). m.p. 130 ^{o}C (dec.); R_f 0.68 (50% EtOAc in petrol); IR (thin film) 3039, 1751, 1717, 1454, 1193, 789, 724, 702 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (3H, t, *J* = 7.2, C*H*$_3$), 3.60 (1H, d, *J* = 17.9, CH*H*), 4.12 – 4.26 (3H, m, C*H*$_2$CH$_3$, C*H*H), 4.33 (1H, m, C*H*), 4.41 (1H, d, *J* = 2.2, C*H*), 4.86 (1H, d, *J* = 11.9, CH*H*), 4.91 (1H, d, *J* = 11.9, C*H*H), 5.11 – 5.15 (1H, m, =C*H*), 7.26 – 7.43 (5H, m, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2 (CH_3), 44.7 (CH_2), 47.6 (CH), 59.9 (C), 60.0 (CH), 61.4 CH_2), 71.77 (CH_2), 101.1 (CH), 127.6 (CH), 128.4 (CH), 128.6 (CH), 135.4 (C), 158.4 (C), 168.5 (C); MS (ES$^+$) *m/z* 310 [M+Na]$^+$, 597 [2M+Na]$^+$; HRMS (ES$^+$) Calc. For $C_{16}H_{17}NNaO_4$ expect 310.1050, Found 310.1053

(5-Methoxy-3-oxo-2-aza-bicyclo[2.2.0]hex-5-en-2-yl)-acetic acid ethyl ester (180)



A novel compound synthesised using modified alkylation conditions.[186] Lactam **167** (50 mg, 0.40 mmol, 1.0 eq), ethyl bromoacetate (67 mg, 0.40 mmol, 1.0 eq) and potassium carbonate (500 mg, 4.00 mmol, 10 eq) were dissolved in DMF (1.2 mL) and stirred at room temperature overnight. The mixture was diluted with ammonium chloride (15 mL) and extracted with dichloromethane (3 x 7.5 mL). The combined organics were washed with water (6 x 5 mL), brine (5 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (20 - 30% EtOAc in petrol + 0.1% triethylamine) yielded **180** as a colourless oil (32 mg, 38%). R_f = 0.3 (30% EtOAc in petrol + 0.1% triethylamine); IR (thin film) 1741, 1612, 1454, 1029 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 1.30 (3H, t, *J* = 7.2, CH_3), 3.71 (3H, s, CH_3), 3.73 (1H, d, *J* = 17.6, CH*H*), 4.11 (1H, d, *J* = 17.6, CH*H*), 4.20 (2H, q, *J* = 7.2, CH_2), 4.30 (1H, dd, *J* = 2.4, 1.1, C*H*), 4.38 (1H, d, *J* = 2.4, C*H*), 5.27 (1H, d, *J* = 1.1, =C*H*) ; ^{13}C NMR (100 MHz, acetone-d_6) δ 14.5 (CH_3), 45.2 (CH_2), 47.8 (CH), 57.2 (CH_3), 59.6 (C), 60.4 (CH), 61.6 (CH_2), 101.3 (CH), 159.2 (C), 169.2 (C=O); MS (ES^+) *m/z* 234 $[M+Na]^+$, 445 $[2M+Na]^+$; HRMS (ES^+) Calc. For $C_{16}H_{14}NO_4$ = 212.0917 $[M+H]^+$, Found 212.0919.

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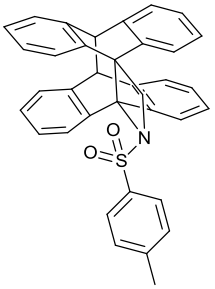
APPENDIX 1 – Calculation of Activation Parameters



T_c Calculations Method

$\Delta G^{\ddagger}$ at coalescence $$\Delta G^{\ddagger} = RTc[23 + \ln(\frac{Tc}{\Delta \nu})]$$

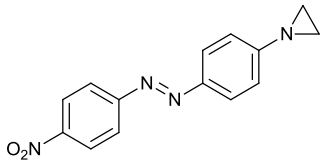
Where $\Delta G^{\ddagger}$ is the Gibbs free energy of activation, R is the gas constant, T_c is the coalescence temperature in Kelvin and $\Delta\nu$ is the shift separation in Hz of the fully resolved exchanging signals.

Where T_c = 188 K and $\Delta\upsilon$ = 373.2 Hz at 178 K

$$\Delta G^{\ddagger} @ 188 \text{ K} = 34.8 \text{ KJ mol}^{-1}$$

Line Shape Fitting Method

Insufficient NMR data obtainable in the slow regime to calculate position of υ_A and υ_B



T_c Calculations Method

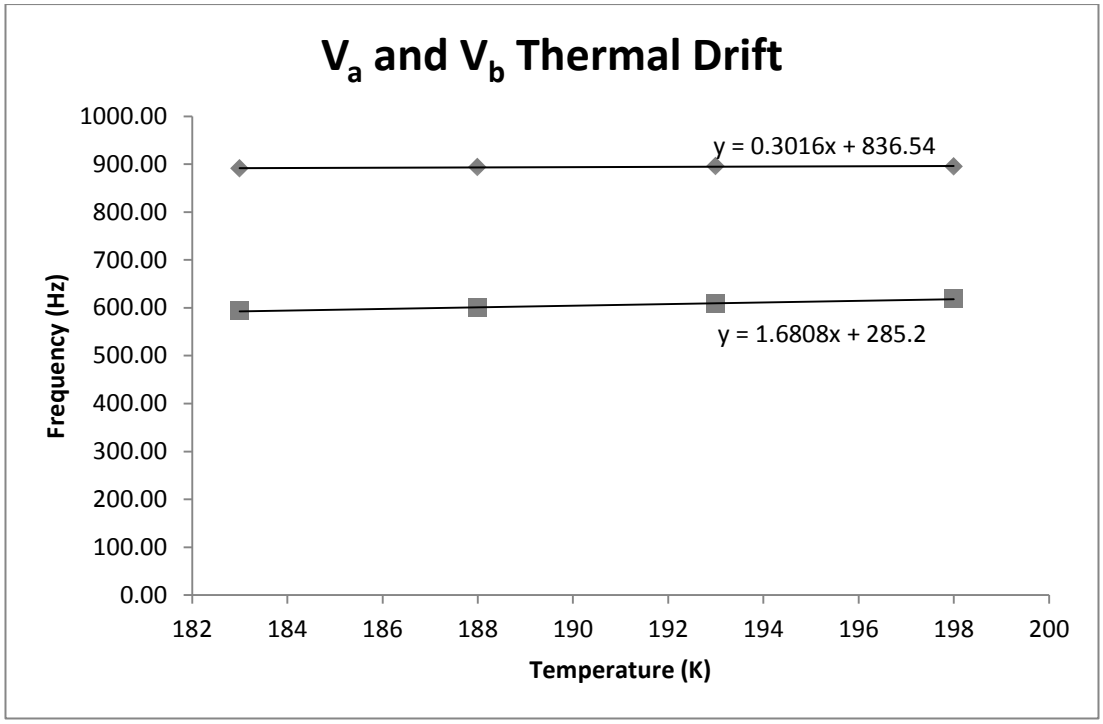
$\Delta G^{\ddagger}$ at coalescence $$\Delta G^{\ddagger} = RTc[23 + \ln(\frac{Tc}{\Delta \nu})]$$

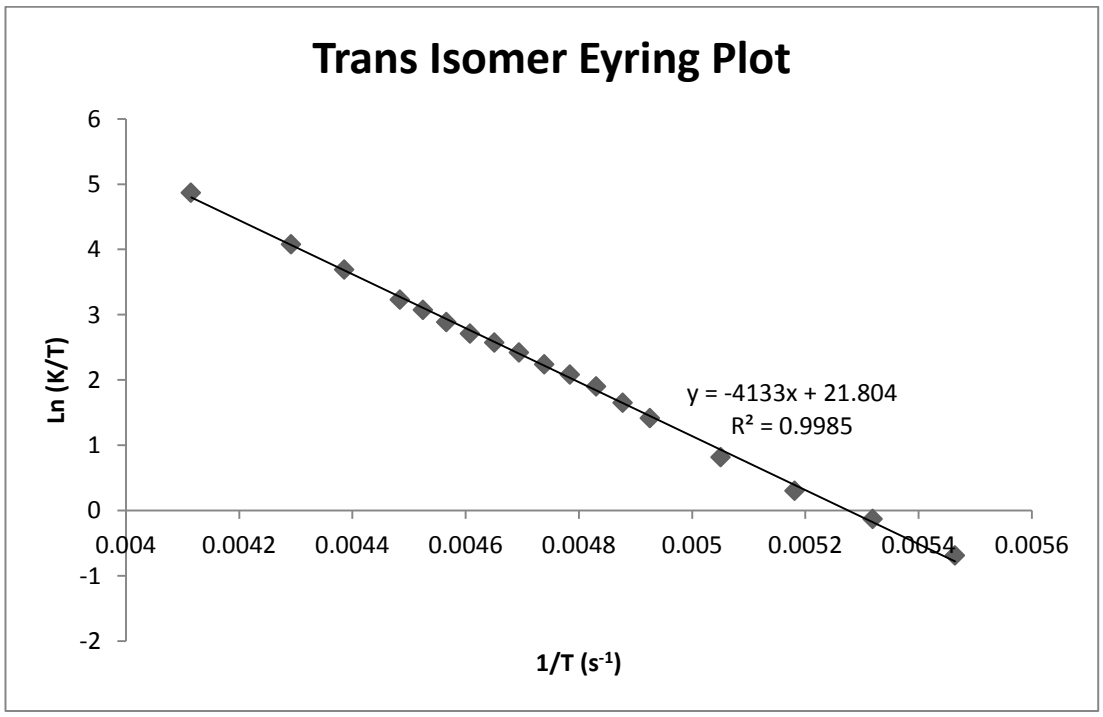
Where T_c = 207 K and $\Delta\upsilon$ = 296.7 Hz at 183 K

$$\Delta G^{\ddagger} \text{ @ 207 K} = 38.9 \text{ kJ mol}^{-1}$$

Line Shape Fitting Method

T (K)	va obs	vb obs	va calc	vb calc	va-vb calc	va-vb obs	Rate K	1/T	Ln K	Ln (K/T)
183	890.80	594.00	891.73	592.79	298.95	296.80	92.00	0.0055	4.5218	-0.6877
188	894.00	600.00	893.24	601.19	292.05	294.00	165.00	0.0053	5.1059	-0.1305
193	896.00	608.35	894.75	609.59	285.15	287.65	261.00	0.0052	5.5645	0.30183
198	895.16	619.23	896.26	618.00	278.26	275.93	447.30	0.0051	6.1032	0.81496
203			897.76	626.40	271.36		833.40	0.0049	6.7255	1.41231
205			898.37	629.76	268.60		1069.50	0.0049	6.9749	1.65194
207			898.97	633.13	265.85		1387.50	0.0048	7.2353	1.90254
209			899.57	636.49	263.09		1674.30	0.0048	7.4232	2.08082
211			900.18	639.85	260.33		1974.30	0.0047	7.588	2.23611
213			900.78	643.21	257.57		2394.40	0.0047	7.7809	2.4196
215			901.38	646.57	254.81		2811.50	0.0047	7.9415	2.57084
217			901.99	649.93	252.05		3263.50	0.0046	8.0906	2.71066
219			902.59	653.30	249.30		3921.60	0.0046	8.2743	2.88518
221			903.19	656.66	246.54		4771.60	0.0045	8.4704	3.07227
223			903.80	660.02	243.78		5641.70	0.0045	8.6379	3.23077
228			905.30	668.42	236.88		9141.70	0.0044	9.1206	3.69126
233			906.81	676.83	229.99		13761.60	0.0043	9.5296	4.0786
243			909.83	693.63	216.19		31611.70	0.0041	10.361	4.86822


V_a and V_b Thermal Drift
y = 0.3016x + 836.54
y = 1.6808x + 285.2
Frequency (Hz)
Temperature (K)
1000.00
900.00
800.00
700.00
600.00
500.00
400.00
300.00
200.00
100.00
0.00
182
184
186
188
190
192
194
196
198
200


Trans Isomer Eyring Plot
y = -4133x + 21.804
R² = 0.9985
Ln (K/T)
1/T (s-1)
6
5
4
3
2
1
0
-1
-2
0.004
0.0042
0.0044
0.0046
0.0048
0.005
0.0052
0.0054
0.0056

$\Delta H^{\ddagger}$ can be calculated from the gradient and $\Delta S^{\ddagger}$ from the intercept using the linear form of the Eyring equation.

$$\ln(k/T) = -\frac{\Delta H^{\ddagger}}{R}\frac{1}{T} + \ln\frac{k_B}{h} + \frac{\Delta S^{\ddagger}}{R}$$

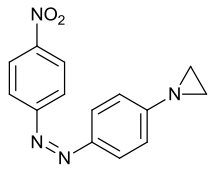
$$y = mx + c$$

Where: *k* is the rate constant in s^{-1}, T is the temperature in Kelvin, k_B is the boltzman constant, h is planks constant, R is the gas constant, $\Delta G^{\ddagger}$ is the Gibbs free energy of activation, $\Delta H^{\ddagger}$ is the enthalpy energy of activation, $\Delta S^{\ddagger}$ is the entropy of activation.

$\Delta G^{\ddagger}$ can then be calculated at any temperature using the constant temperature Gibbs free energy relationship.

$$\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$$

$\Delta H^{\#}$ (kJ/mol)	34.4
$\Delta S^{\#}$ (J/Kmol)	-16.3
$\Delta G^{\#}$ (at 298)	39.2
$\Delta G^{\#}$ (at 207)	37.7
$\Delta G^{\#}$ (at 223)	38.0



T_c Calculations Method

$\Delta G^{\ddagger}$ at coalescence $$\Delta G^{\ddagger} = RTc[23 + \ln(\frac{Tc}{\Delta \nu})]$$

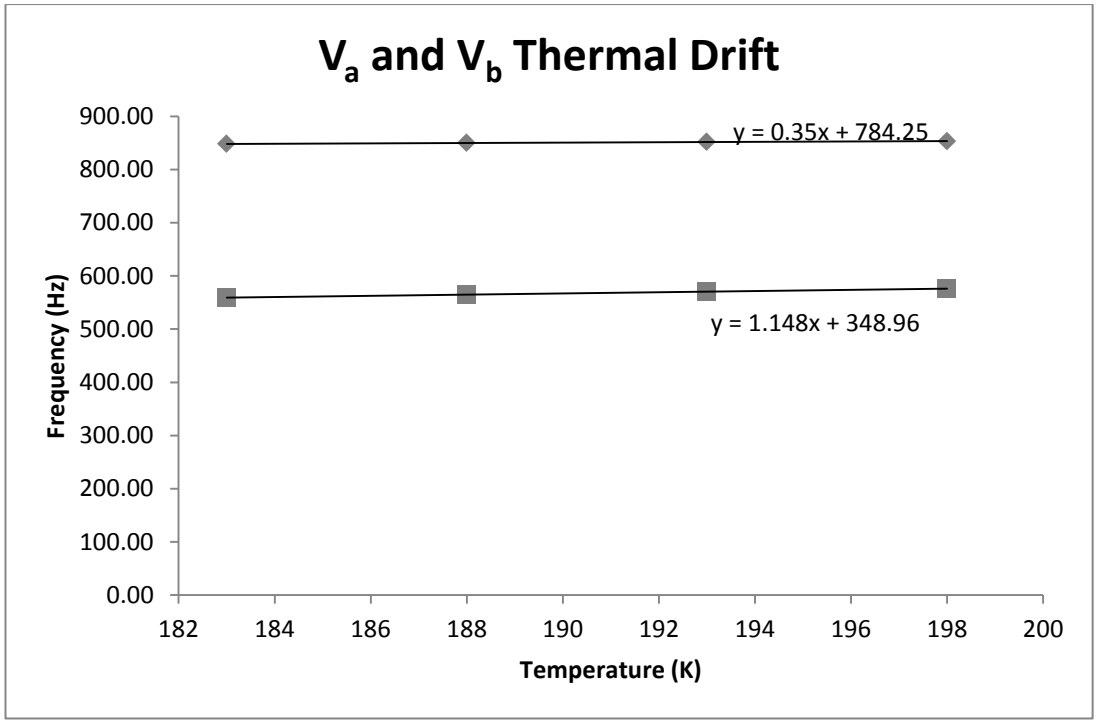
Where T_c = 223 K and $\Delta\upsilon$ = 288.9 Hz at 183 K

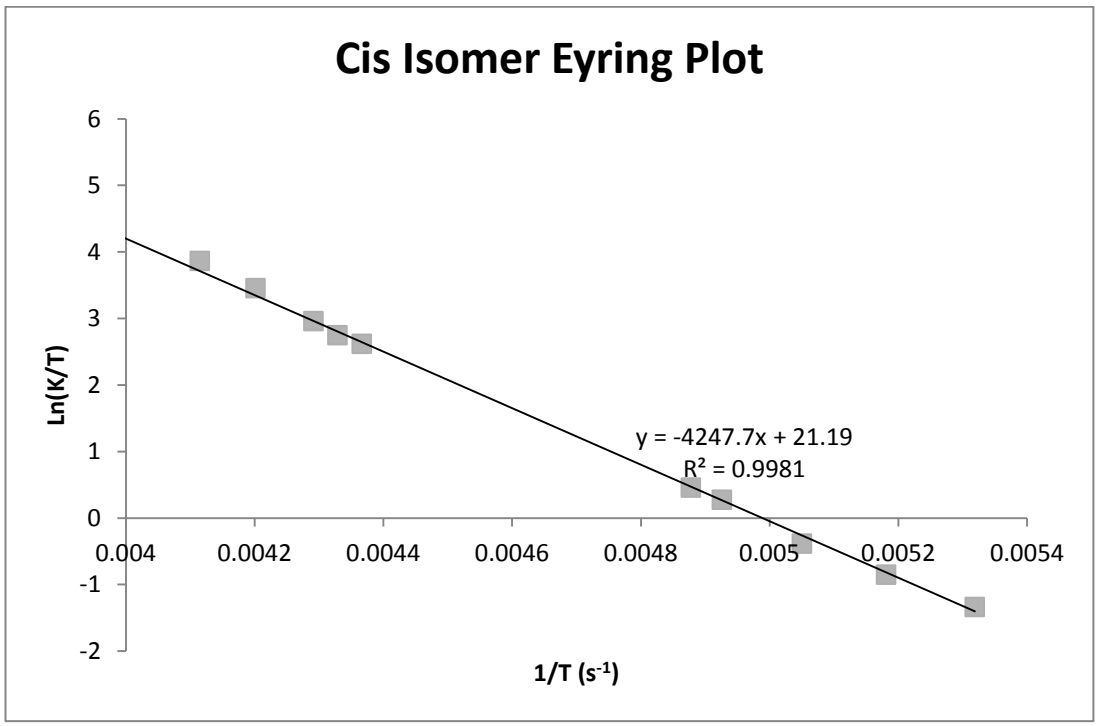
$$\Delta G^{\ddagger} \text{ @ 223 K} = 42.2 \text{ kJ mol}^{-1}$$

Line Shape Fitting Method

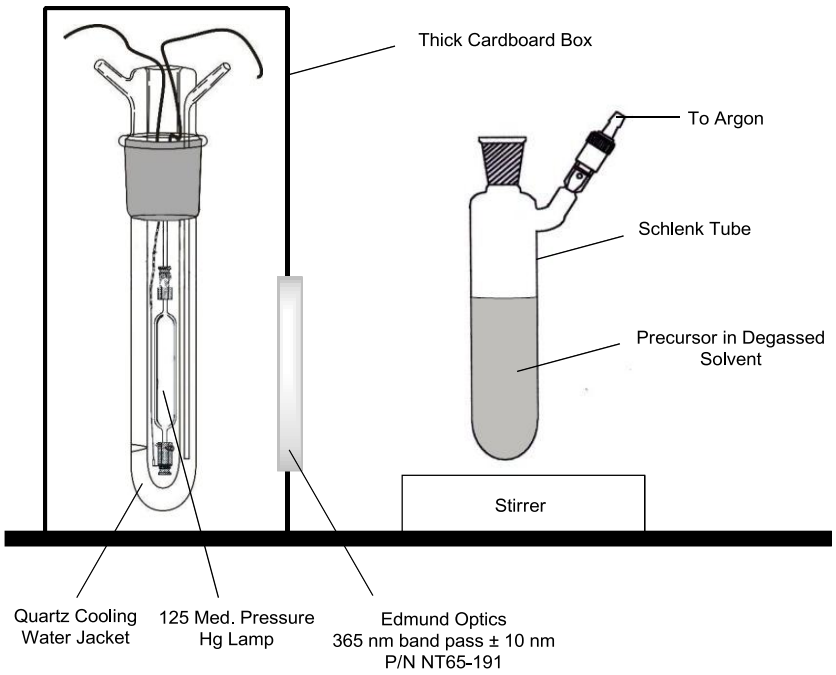
T (K)	va obs	vb obs	va calc	vb calc	va-vb calc	va-vb obs	Rate K	1/T	Ln K	Ln (K/T)
183	848.20	558.40	848.30	559.04	289.26	289.80	46.30	0.0055	3.8351	-1.374
188	850.10	565.50	850.05	564.78	285.27	284.60	49.40	0.0053	3.9	-1.336
193	852.00	571.00	851.80	570.52	281.28	281.00	82.50	0.0052	4.4128	-0.85
198	853.40	575.70	853.55	576.26	277.29	277.70	134.60	0.0051	4.9023	-0.386
203			855.30	582.00	273.30		266.70	0.0049	5.5861	0.2729
205			856.00	584.30	271.70		323.80	0.0049	5.7801	0.4571
229			864.40	611.85	252.55		3133.80	0.0044	8.05	2.6163
231			865.10	614.15	250.95		3603.80	0.0043	8.1897	2.7473
233			865.80	616.44	249.36		4493.80	0.0043	8.4105	2.9594
238			867.55	622.18	245.37		7553.80	0.0042	8.9298	3.4575
243			869.30	627.92	241.38		11583.80	0.0041	9.3574	3.8643
253			872.80	639.40	233.40		23342.80	0.004	10.058	4.5247
263			876.30	650.88	225.42		40502.80	0.0038	10.609	5.037
273			879.80	662.36	217.44		61232.80	0.0037	11.022	5.413

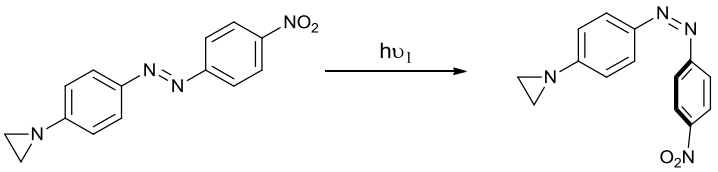
$\Delta H^{\#}$ (kJ/mol)	35.3
$\Delta S^{\#}$ (J/Kmol)	-21.4
$\Delta G^{\#}$ (at 298)	41.7
$\Delta G^{\#}$ (at 207)	39.7
$\Delta G^{\#}$ (at 223)	40.1

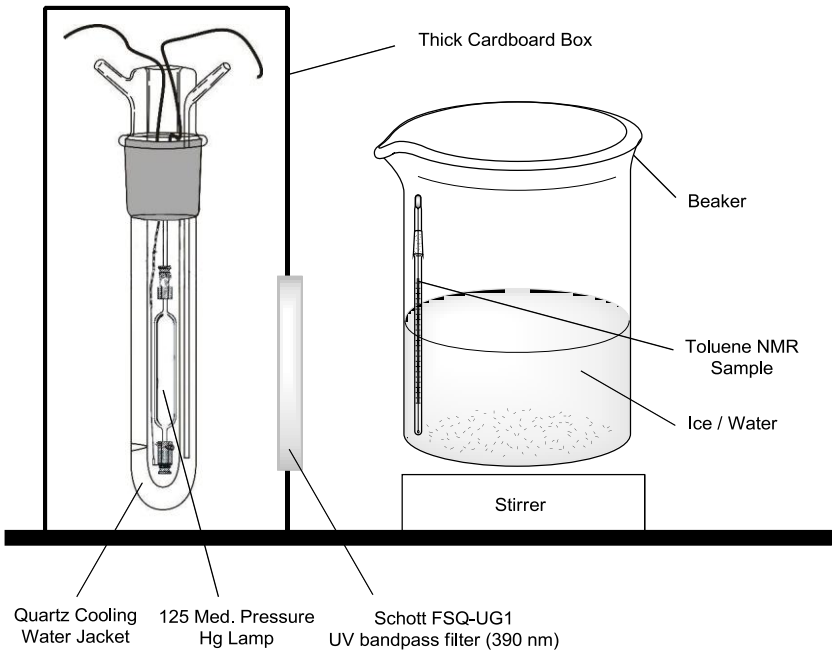

V_a and V_b Thermal Drift
y = 0.35x + 784.25
y = 1.148x + 348.96
Frequency (Hz)
900.00
800.00
700.00
600.00
500.00
400.00
300.00
200.00
100.00
0.00
182
184
186
188
190
192
194
196
198
200
Temperature (K)

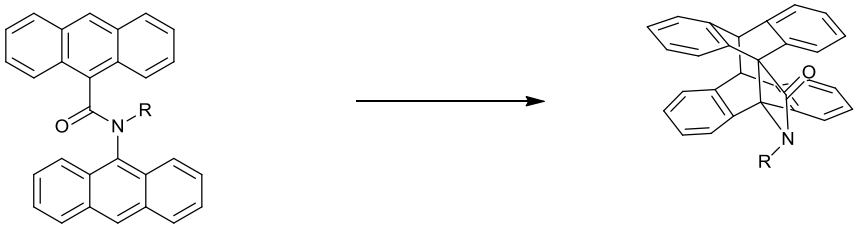

Cis Isomer Eyring Plot
y = -4247.7x + 21.19
R² = 0.9981
Ln(K/T)
6
5
4
3
2
1
0
-1
-2
0.004
0.0042
0.0044
0.0046
0.0048
0.005
0.0052
0.0054
1/T (s-1)

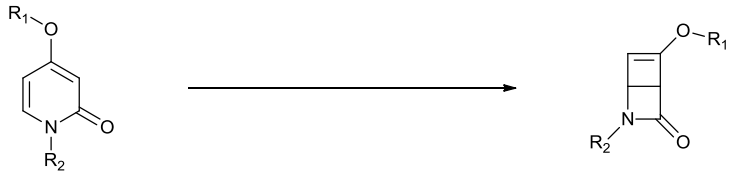
APPENDIX 2 – Photochemical Experimental Setups

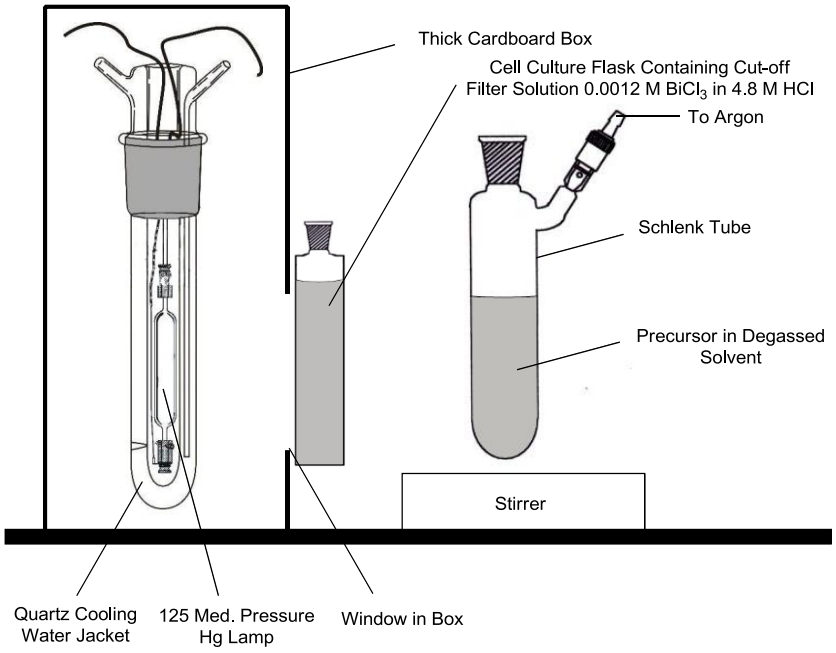



NO2
hυ1
N
N
N
N
O2N

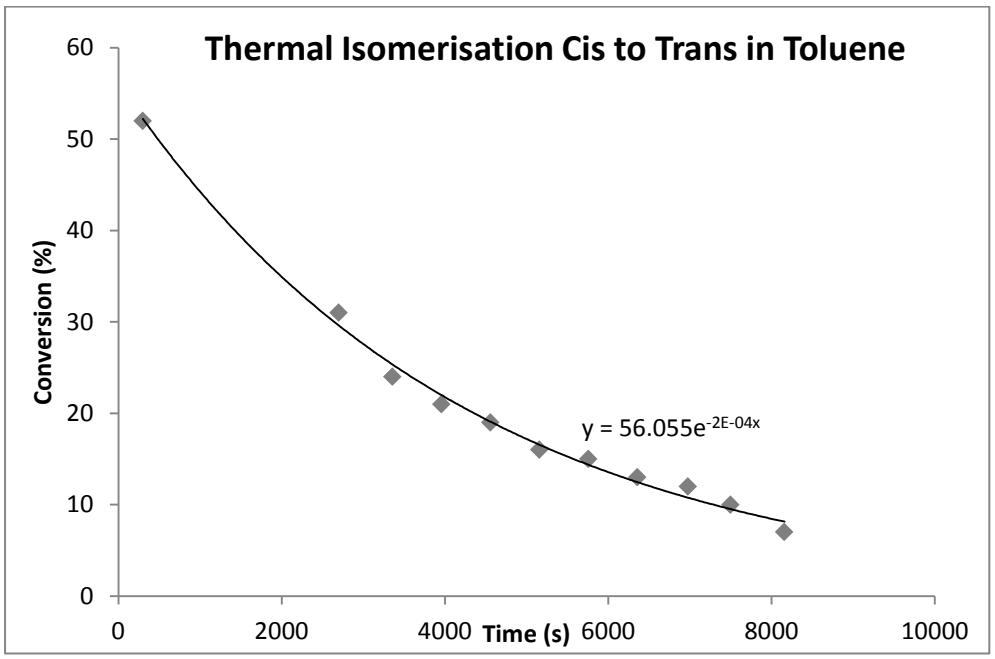

Thick Cardboard Box
Beaker
Toluene NMR Sample
Ice / Water
Stirrer
Quartz Cooling Water Jacket
125 Med. Pressure Hg Lamp
Schott FSQ-UG1 UV bandpass filter (390 nm)


O
N
R
O
N
R

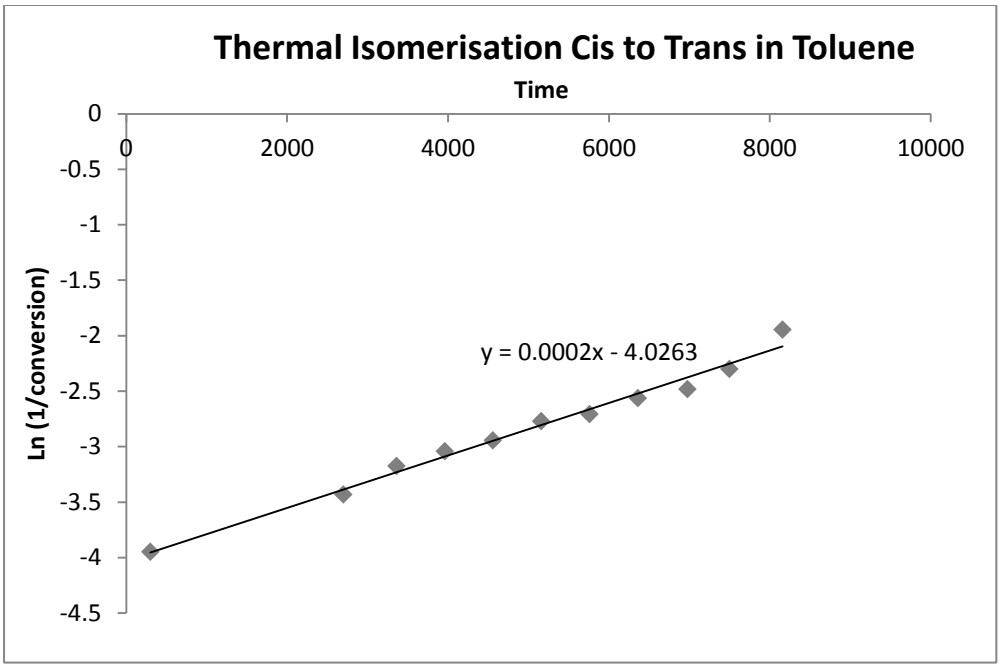

R1
O
N
O
R2
O
R1
N
R2
O


Thick Cardboard Box
Cell Culture Flask Containing Cut-off Filter Solution 0.0012 M BiCl3 in 4.8 M HCl
To Argon
Schlenk Tube
Precursor in Degassed Solvent
Stirrer
Quartz Cooling Water Jacket
125 Med. Pressure Hg Lamp
Window in Box

Appendix 3 – Isomerisation Rate Data



Regeneration of *trans*-**90** measured by integration of the well separated aziridine ^{1}H NMR signals at 1.56 ppm in the *cis* isomer and 1.66 in the *trans* isomer.



Determination of the rate constant.